(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

A04

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25238 A2

(51) International Patent Classification[7]: C07D 471/04, 513/04, 498/04, A61K 31/437, 31/4355, A61P 35/00, C07D 217/24 // (C07D 471/04, 235:00, 221:00) (C07D 513/00, 277:00, 221:00)

(21) International Application Number: PCT/US00/27444

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/157,922 6 October 1999 (06.10.1999) US

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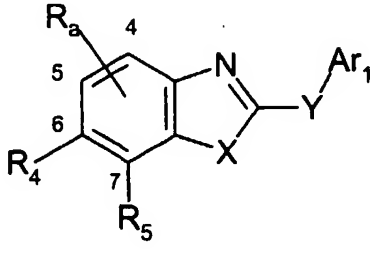
(81) Designated States *(national)*: CA, JP, MX.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCYCLIC COMPOUNDS USEFUL AS INHIBITORS OF TYROSINE KINASES



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(57) Abstract: Disclosed are novel compounds of formula (I) wherein Ar_1, R_a, R_4, R_5, X and Y are defined below, which are useful as inhibitors of certain protein tyrosina kinases and are thus useful for treating diseases associated with such kinases, for example, diseases resulting from inappropriate cell proliferation, which include autoimmune diseases, chronic inflammatory diseases, allergic diseases, transplant rejection and cancer. Also disclosed are processes for preparing these compounds, novel intermediates useful in these processes and compositions comprising compounds of formula (I).

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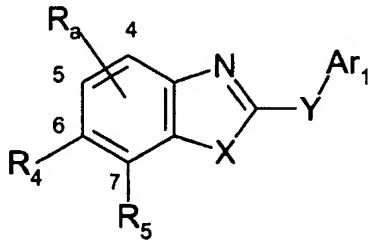
HETEROCYCLIC COMPOUNDS USEFUL AS INHIBITORS OF TYROSINE KINASES

Benefit is hereby claimed from U.S. Provisional Application No. 60/157,922, filed October 6, 1999, herein incorporated by reference in its entirety.

Technical Field of the Invention

This invention relates to substituted compounds of formula (I):



(I)

wherein Ar_1, R_a, R_4, R_5, X and Y are defined below, which are useful as inhibitors of certain protein tyrosine kinases and are thus useful for treating diseases resulting from inappropriate cell proliferation, which include autoimmune diseases, chronic inflammatory diseases, allergic diseases, transplant rejection and cancer. This invention also relates to processes for preparing these compounds and to pharmaceutical compositions comprising these compounds.

Background of the Invention

Tyrosine kinases play an essential role in the regulation of cell signaling and cell proliferation by phosphorylating tyrosine residues of peptides and proteins. Inappropriate activation of tyrosine kinases is known to be involved in a variety of disease states, including immunologic and oncologic disorders.

It has been well established that T cells play an important role in regulating the immune response (F. Powrie and R.L. Coffman, *Immunol. Today*, **1993**, *14*, 270). Activation of T cells is often the initiating event in many inflammatory and autoimmune diseases. In addition to their role in immune surveillance, T cells can become autoreactive by recognizing self-antigens and thereby cause autoimmune disease such as rheumatoid arthritis and inflammatory bowel disease.

The T cell receptor (TCR) is the antigen-specific component of the T cell and is activated when the receptor is engaged with foreign or self-antigenic peptides. When the TCR is activated a series of enzyme-mediated signal transduction cascades is initiated which results in the production of pro-inflammatory cytokines such as interleukin-2 (IL-2).

The release of IL-2 is critically important since this lymphokine is required for T-lymphocyte proliferation, differentiation, and effector function. Clinical studies have shown that interference with IL-2 activity effectively suppresses immune response *in vivo* (T.A. Waldmann, *Immunol. Today*, 1993, *14*, 270). Accordingly, agents which inhibit T-lymphocyte activation and subsequent IL-2 production, or block the activity of IL-2 are therapeutically useful for selectively suppressing immune response in a patient in need of such immunosuppression.

The eight members of the src family of tyrosine kinases are src, lck, fyn, lyn, hck, fgr, blk and yes (J.B. Bolen, J.S. Brugge, *Ann. Rev. Immunol.*, **1997**, *15*, 371). These can be divided into 2 groups based on their pattern of tissue expression. Src, fyn and yes have a

broad distribution while expression of lck, lyn, hck, fgr, and blk is largely limited to hemopoietic cells. The therapeutic effects of inhibiting kinases of the src family can be ascertained by linking functional defects seen in gene disruption studies in mice. Src(-/-) mice had severe abnormalities in bone remodeling. Inhibition of src may therefore be useful in treating osteoporosis. Lck(-/-) mice display a complete lack of CD4+ cells and are unable to mount antigen-dependent immune responses.

A kinase of particular interest is p56lck, which is only expressed in T-cells. Within the TCR signal transduction cascade the tyrosine kinase p56lck is a required element to initiate the activation response from the TCR intracellular domains to other signaling proteins. For example, T cells which lack the p56lck protein are unable to signal through the T cell receptor (D.B. Straus and A. Weiss, *Cell*, 1992, *70*, 585). Transfection of p56lck back into these cell lines restores TCR responsiveness. Also, it has been shown in mice that inactivation of the p56lck gene leads to lack of proper thymocyte development (T.J. Molina et al., *Nature*, 1992, *357*, 161).

The conclusion drawn from these studies is that p56lck plays a crucial role in T cell maturation and antigen-induced T-cell activation. Therefore, an agent blocking p56lck would effectively block T cell function, act as an immunosuppressive agent and have potential utility in autoimmune diseases, for example rheumatoid arthritis, multiple sclerosis, lupus, transplant rejection and allergic diseases (J.H. Hanke et al., *Inflamm. Res.*, **1995**, *44*, 357).

Inhibitors of other members of the src family of non-receptor tyrosine kinases are also useful for treating various disease states. Src is present in osteoclasts, and is important in bone remodeling. For example, inactivation of p60src diminishes bone resorption by osteoclasts (P. Soriano et al., *Cell* 1991, *64*, 693, B.F. Boyce et al. *J. Clin. Invest* **1992**, *90*, 1622), it is therefore possible that inhibitors of the kinase activity of p60src are useful in the treatment of osteoporosis, Paget's disease and inflammation of bones and joints.

Src kinases have been found to be activated in tumors, including breast and colon cancers, melanoma and sarcoma. For example, a number of primary tumors and tumor cell lines from patients with breast cancer, colon cancer, melanoma and sarcoma have been shown to have elevated src kinase activity, and activating src mutations are seen in some advanced colon cancers. Inhibitors of src kinase had significant antiproliferative activity against cancer cell lines (M.M. Moasser et al., *Cancer Res.*, 1999, *59*, 6145) and inhibited the transformation of cells to an oncogenic phenotype (R. Karni et al., *Oncogene*, 1999, *18*, 4654) suggesting that src kinase inhibitors may be useful anti-cancer agents.

In addition, src family kinases participate in signal transduction in several cell types. For example, fyn, like lck, is involved in T-cell activation. Hck and fgr are involved in Fc gamma receptor mediated oxidative burst of neutrophils. Src and lyn are believed to be important in Fc epsilon induced degranulation of mast cells, and so may play a role in asthma and other allergic diseases. The kinase lyn is known to be involved in the cellular response to DNA damage induced by UV light (T. Hiwasa, *FEBS Lett.* **1999**, *444*, 173) or ionizing radiation (S. Kumar, *J. Biol Chem*, **1998**, *273*, 25654). Inhibitors of lyn kinase may thus be useful as potentiators in radiation therapy.

Platelet derived growth factor is a potent mitogen for smooth muscle cells. Its receptor (PDGFR) is a member of the receptor tyrosine kinase family (L. Claesson-Welsh, *J. Biol Chem*, **1994**, *269*, 32023). PDGF is involved in atherosclerosis and restenosis (K.E. Bornfeldt, *Trends Cardiovasc. Med.*, **1996**, *6*, 143). In addition, receptor tyrosine kinases including PDGFR kinase have been implicated as contributing factors in cancer (A. Levitzki and A. Gazit, *Science*, 1995, *267*, 1782) including ovarian (M.B. Dabrow et al., *Gynecologic Oncology*, 1998, *71*, 29) and prostate (S.M. Sintich et al., *Endocrinology*, 1999, *140*, 3411) cancers and glioblastoma (B.J. Silver, *BioFactors,* **1992** *3*, 217). Inhibitors of PDGFR kinase are thus useful in the treatment of fibrotic diseases, restenosis and PDGF-dependent tumors.

Reports have appeared in the literature of agents that inhibit the kinase activity of p56lck kinase and thus inhibit T cell activation. These include the natural product lavendustin A, and analogs (M.S. Smyth, *J. Med. Chem.*, **1993**, *36*, 3010), the natural product damnacanthal (C.R. Faltynek et al., *Biochemistry*, **1995**, *34*, 12404), and a 1-methoxy agroclavine isolated from a fungal extract (R. Padmanabha et al. *Bioorganic and Med. Chem. Letters*, 1998, *8*, 569). Other inhibitors reported include WIN 61651 *(J. Enzyme Inhibition*, **1995**, *9*, 111) pyrazolopyrimidines PP1 and PP2 (Hanke et al. *J. Biol Chem*, **1996**, *271*, 695) and indanone and indandione derivatives (J.L. Bullington et al., *Bioorganic and Med. Chem. Letters*, **1998**, *8*, 2489).

A.P. Spader et al. (WO 98/54157, 1998) describe quinoline and quinoxaline compounds that inhibit p56lck and PDGFR kinase. Fused polycyclic 2-aminopyrimidine derivatives that inhibit p56lck are reported by J.M. Davis et al. (WO 98/28281, 1998). J. Das et al. claim a series of benzothiazole amides as inhibitors of lck and other src family kinases (WO 99/24035, 1999). Inhibitors of PDGFR kinase and src-family kinases were reviewed by H.D.H. Showalter, A.J. Kraker, *Pharmacol. Ther.*, **1997**, *76*, 55. Several patents on inhibitors of lck are reviewed in P.M. Traxler, *Exp. Opin. Ther. Patents*, 1997, 7, 571,and P.M. Traxler, *Exp. Opin. Ther. Patents*, 1998, 8, 1599.

U.S. Pat. No. 4,176,184 discloses imidazoisoquinoline-diones, which are described as being useful as cardiotonics, hypotensives, antithrombotics and antiarrhythmics. DE 3410168 A1 discloses imidazoisoquinoline-dione derivatives, these compounds are described as being useful as cardiotonic agents in which the substituent on the fused imidazole ring is a pyridine ring bridged to the imidazole carbon by a C_1-C_4 alkyl group, a vinyl group or a chemical bond. EP 322 746 A1 discloses heterocyclic lactam derivatives described as being useful as cardiotonic agents, antihypertensive agents and vasodilators.

The compounds of the present invention represent a novel structural class, which is distinct from previously reported tyrosine kinase inhibitors.

Brief Summary of the Invention

The work cited above supports the principle that inhibition of the kinases mentioned above will be beneficial in the treatment of various disease states.

It is therefore an object of the invention to provide novel compounds which inhibit PDGFR kinase and the src-family kinases including lck, src, fyn, lyn, hck, fgr, blk and yes.

It is a further object of the invention to provide methods for treating diseases and pathological conditions mediated by src-family tyrosine kinases and PDGFR kinase such as autoimmune diseases, transplant rejection, psoriasis, osteoporosis, Paget's disease, cancer, including src-dependent tumors and PDGF-dependent tumors, atherosclerosis, restenosis and allergic diseases, using the novel compounds of the invention.

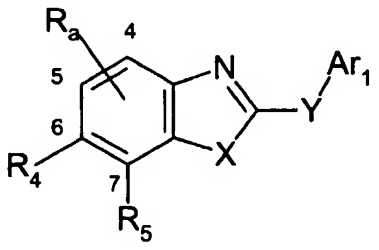
It is yet a further object of the invention to provide processes of preparation of the above-mentioned novel compounds and pharmaceutical compositions comprising the same.

Detailed Description of the Invention

The src-family tyrosine kinases and PDGFR kinase discussed above exhibit some homology in their amino acid structure. It is contemplated that due to structural differences between individual src-family kinases and PDGFR kinase, different compounds of the invention may have different inhibitory potencies against individual tyrosine kinases. Thus some of compounds of the invention may also be expected to be most effective in treating diseases mediated by tyrosine kinases that they inhibit most potently. Particular compounds disclosed herein have been shown to be active inhibitors

of p56lck kinase, p60src kinase and PDGFR kinase. See the section entitled "Assessment of Biological Properties" disclosed herein.

In its broadest generic aspect, the invention provides novel compounds of the formula I:



(I)

wherein:

Ar_1 is an aromatic or nonaromatic carbocycle, heteroaryl or heterocycle; wherein said carbocycle, heteroaryl or heterocycle is optionally substituted by one or more R_1, R_2 and R_3;

X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

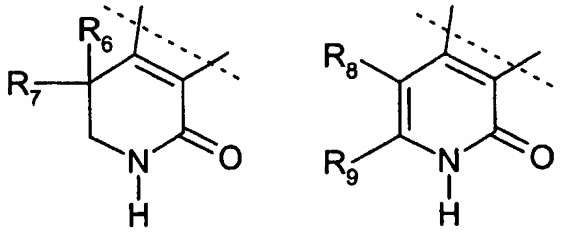
Y is NR_{15}, S or O;

R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl; wherein each R_a is independently optionally substituted with one or more C_{1-6}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl, each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5- position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $CONR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$, $(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$; or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H, CN or $CONR_{10}R_{11}$; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10}cycloalkyl, C_{5-7}cycloalkenyl, C_{2-6} alkenyl, C_{2-6} alkynyl each being optionally substituted with one or more C_{3-10}cycloalkyl, C_{3-10}cycloalkylidene, C_{5-7}cycloalkenyl, halogen, OH, oxo, CN, C_{1-3}alkoxy, C_{1-3}acyloxy, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}C(=NR_{10})NR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$, $C(R_{10})=NNR_{10}CONR_{10}R_{11}$, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy, arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl, heteroaryl, or heterocycle, wherein each aryl, heteroaryl or heterocycle is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl or $NR_{10}C(=NR_{10})NR_{10}R_{11}$, C_{1-3}alkoxy, halogen, CN, oxo, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 5 or 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two C_{1-3}alkyl, OH, oxo or $(CH_2)_nNR_{10}R_{11}$, or optionally spiro-fused to a 1,3 dioxolane group or 1,3 dithiolane group, each 1,3 dioxolane group or 1,3 dithiolane group optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, CN, NO_2, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$, and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH, $-(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or heterocycle, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

R_{15} is H or C_{1-3} alkyl;

m is 1-4; n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

In one embodiment of the invention, there are provided compounds of the formula (I) described above, wherein:

Ar_1 is

a) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl;

b) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cycloheptenyl;

c) phenyl, naphthyl; indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl;

d) heteroaryl selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, benzothiazolyl, quinazolinyl, and indazolyl,or a fused heteroaryl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; or

e) a heterocycle selected from pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl and indolinyl;

wherein each of the above Ar_1 are optionally substituted by one or more R_1, R_2 and R_3;

R_a is H, C_{1-6}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, phenyl or heteroaryl selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, pyrazolyl, imidazolyl, furyl, thiazolyl and thienyl; each R_a being optionally substituted with one or more phenyl, halogen, C_{1-3}alkyl, C_{1-3} alkoxy, OH, oxo, or $NR_{10}R_{11}$; wherein R_a is at the 4- position;

R_1 and R_2 are as hereinabove defined;

R_3 is H, halogen, methyl, methoxy, hydroxymethyl or OH;

R_8 is H, C_{1-3}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$ or $(CH_2)_nCONR_{10}R_{11}$;

R_9 is CN or $CONR_{10}R_{11}$; or R_9 is C_{1-3}alkyl branched or unbranched, C_{2-4} alkenyl, C_{2-4}alkynyl each being optionally substituted with one or more C_{5-7}cycloalkyl, C_{5-7} cycloalkylidene, C_{5-7}cycloalkenyl,OH, CN, C_{1-3}acyloxy, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}C(=NR_{10})NR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$, $C(R_{10})=NNR_{10}CONR_{10}R_{11}$, aryl or heteroaryl; wherein each aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl,heteroaryl or heterocycle, each optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl or $NR_{10}C(=NR_{10})NR_{10}R_{11}$, C_{1-3}alkoxy, halogen, CN, oxo, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 5 or 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by C_{1-3}alkyl or OH, or optionally spiro-fused to a 1,3 dioxolane group or 1,3 dithiolane group, each 1,3 dioxolane group or 1,3 dithiolane group optionally substituted by C_{1-3}alkyl, C_{1-3}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, benzyl and phenyl; wherein said alkyl, cycloalkyl, benzyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CN, NO_2, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH, $-(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;;

R_{12} is H, C_{1-6}alkyl or C_{5-7}cycloalkyl, each optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or heterocycle, each optionally substituted with one

to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;

or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$; and

R_{15} is H.

In another embodiment, there are provided compounds of the formula (I) described immediately above, wherein:

Ar_1 is phenyl, or pyridyl, wherein each is optionally substituted by one or more

R_1, R_2 and R_3 as defined below;

X is NH or N-CH_3;

Y is NH and

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl;

R_1 and R_2 are the same or different and selected from: H, halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl are optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is CN; or R_9 is methyl, C_{2-3} alkenyl or C_{2-3} alkynyl, each being optionally substituted with one or more C_{5-7} cycloalkylidene, C_{5-7}cycloalkenyl, OH, CN, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$ or heteroaryl;

or R_9 is aryl or heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, amino or $CONH_2$;

or R_8 and R_9 together form a cyclopentene ring spiro-fused to a 1,3 dioxolane group, said 1,3 dioxolane group being optionally substituted by C_{1-3}alkyl, C_{1-3}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, C_{5-7}cycloalkyl or phenyl, wherein said alkyl, cycloalkyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, NO_2, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy,OH, $(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-3}alkyl or C_{5-7}cycloalkyl, each optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or is a saturated, 4- to 6-membered nitrogen-containing heterocycle, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

In yet another embodiment, there are provided compounds of the formula (I) described immediately above, wherein:

Ar_1 is phenyl;

R_a is H or hydroxymethyl;

R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

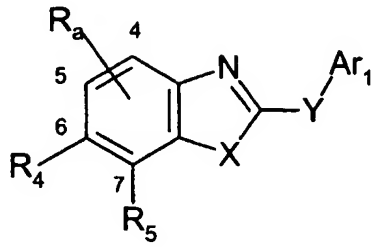
R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched or C_{5-7}cycloalkyl, wherein said alkyl or cycloalkyl are optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl, $NR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino; or R_{12} is phenyl or is azetidinyl, pyrrolidinyl or piperidinyl, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy and halogen.

In another subgeneric aspect, the invention provides novel compounds of the formula I:



(I)

wherein:

Ar_1 is an aromatic or nonaromatic carbocycle, heteroaryl or heterocycle; wherein said carbocycle, heteroaryl or heterocyle is optionally substituted by one or more R_1, R_2 and R_3;

X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

Y is NR_{15}, S or O;

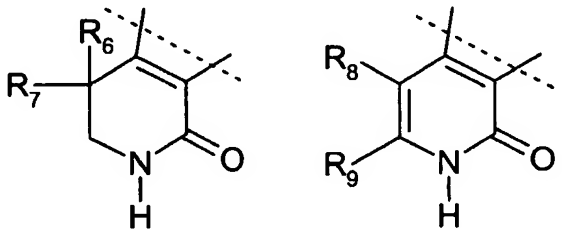
R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl; wherein each R_a is independently optionally substituted with one or more C_{1-3}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5- position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched

alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the above mentioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6} alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$,

$(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$; or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl each being optionally substituted with one or more halogen, OH, oxo, CN, C_{1-3}alkoxy, $NR_{10}R_{11}$, $NR_{10}COR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy, arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl or heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two OH, oxo or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$, and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

R_{15} is H or C_{1-3} alkyl;

m is 1-4, n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

In one embodiment of the invention, there are provided compounds of the formula (I) as described immediately above, and wherein:

Ar_1 is

a) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl;

b) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cycloheptenyl;

c) phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl;

d) heteroaryl selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, benzothiazolyl, quinazolinyl, and indazolyl,or a fused heteroaryl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline,

cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; or

e) a heterocycle selected from: pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl and indolinyl;

wherein each of the above Ar_1 are optionally substituted by one or more R_1, R_2 and R_3 as hereinabove defined;

R_a is H, C_{1-6} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, phenyl or heteroaryl selected from: pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, pyrazolyl, imidazolyl, furyl, thiazolyl and thienyl; each R_a being optionally substituted with one or more phenyl, halogen, C_{1-3}alkyl, C_{1-3} alkoxy, OH, oxo, or $NR_{10}R_{11}$; wherein R_a is at the 4- position;

R_3 is H, halogen, methyl, methoxy, hydroxymethyl or OH;

R_8 is H, C_{1-3}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$ or $(CH_2)_nCONR_{10}R_{11}$;

R_9 is C_{1-3}alkyl branched or unbranched, C_{2-4} alkenyl, C_{2-4}alkynyl each being optionally substituted with one or more OH, CN, $NR_{10}R_{11}$, $CONR_{10}R_{11}$, CO_2R_{12}, aryl or heteroaryl; wherein each aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;
or R_9 is aryl or heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by OH;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, benzyl and phenyl; wherein said alkyl, cycloalkyl, benzyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H or C_{1-6}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;

or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$; and

R_{15} is H.

In another embodiment of the invention, there are provided compounds of the formula (I) as described immediately above, and wherein:

Ar_1 is phenyl, or pyridyl;

X is NH or N-CH_3;

Y is NH and

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl;

R_1 and R_2 are the same or different and selected from: halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl are optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is methyl or C_{2-3} alkenyl each being optionally substituted with one or more OH, CN, $NR_{10}R_{11}$, $CONR_{10}R_{11}$ or CO_2R_{12};
or R_9 is heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen or amino;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy or OH;

R_{12} is H or C_{1-3}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

In yet another embodiment of the invention there are provided compounds of the formula (I) as described immediately above, and wherein:

Ar_1 is phenyl;

R_a is H or hydroxymethyl;

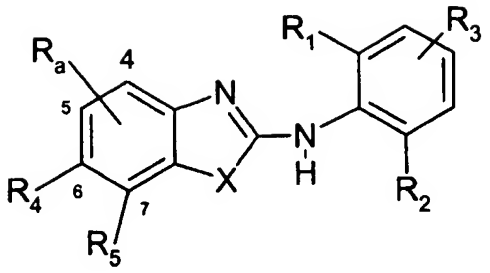
R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;
or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino.

In still another embodiment of the invention there are provided compounds of the formula (Ia):



(Ia)

wherein:

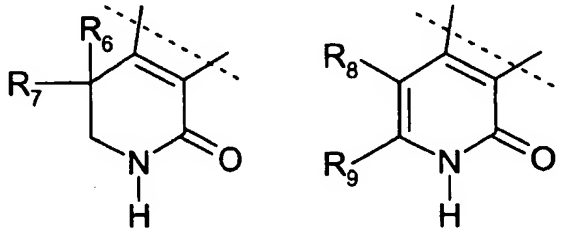
X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl;
wherein each R_a is independently optionally substituted with one or more C_{1-6}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5-position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $CONR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$, $(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$ or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H, CN or $CONR_{10}R_{11}$; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10}cycloalkyl, C_{5-7}cycloalkenyl, C_{2-6} alkenyl, C_{2-6} alkynyl each being optionally substituted with one or more C_{3-10}cycloalkyl, C_{3-10}cycloalkylidene, C_{5-7}cycloalkenyl, halogen, OH, oxo, CN, C_{1-3}alkoxy, C_{1-3}acyloxy, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}C(=NR_{10})NR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$, $C(R_{10})=NNR_{10}CONR_{10}R_{11}$, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy,

arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl, heteroaryl, or heterocycle, wherein each aryl, heteroaryl or heterocycle is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl or $NR_{10}C(=NR_{10})NR_{10}R_{11}$, C_{1-3}alkoxy, halogen, CN, oxo, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 5 or 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two C_{1-3}alkyl, OH, oxo or $(CH_2)_nNR_{10}R_{11}$, or optionally spiro-fused to a 1,3 dioxolane group or 1,3 dithiolane group, each 1,3 dioxolane group or 1,3 dithiolane group optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, CN, NO_2, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$, and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH, $-(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or heterocycle, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

m is 1-4, n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

In another embodiment of the invention, there are provided compounds of the formula (Ia) as described above, wherein:

X is NH or N-CH_3;

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl; and wherein R_a is attached at the 4- position;

R_1 and R_2 are the same or different and selected from: H, halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is CN; or R_9 is methyl, C_{2-3} alkenyl or C_{2-3} alkynyl, each being optionally substituted with one or more C_{5-7} cycloalkylidene, C_{5-7}cycloalkenyl, OH, CN, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, , $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$ or heteroaryl;

or R_9 is aryl or heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, amino or $CONH_2$;

or R_8 and R_9 together form a cyclopentene ring spiro-fused to a 1,3 dioxolane group, said 1,3 dioxolane group being optionally substituted by C_{1-3}alkyl, C_{1-3}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, C_{5-7}cycloalkyl or phenyl, wherein said alkyl, cycloalkyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, NO_2, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy,OH, $(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-3}alkyl or C_{5-7}cycloalkyl, each optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or is a saturated, 4- to 6-membered nitrogen-containing heterocycle, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

In yet another embodiment of the present invention, there are provided compounds of the formula (Ia) described immediately above, wherein:

R_a is H or hydroxymethyl;

R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

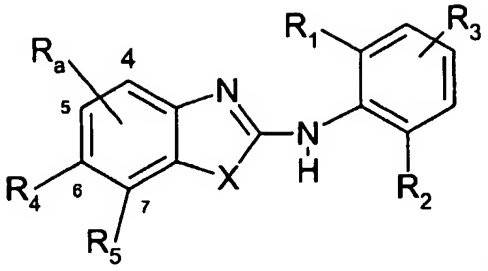
R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched or C_{5-7}cycloalkyl, wherein said alkyl or cycloalkyl are optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl, $NR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino; or R_{12} is phenyl or is azetidinyl, pyrrolidinyl or piperidinyl, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy and halogen.

In still another subgeneric embodiment of the invention there are provided compounds of the formula (Ia):



(Ia)

wherein:

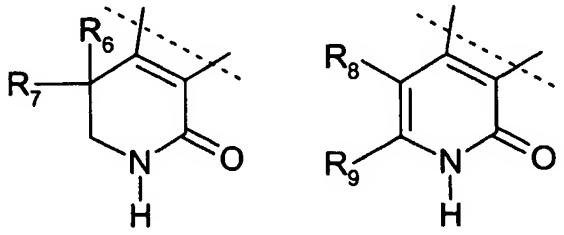
X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl;
wherein each R_a is independently optionally substituted with one or more C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5- position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the above mentioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$, $(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$ or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10}cycloalkyl, C_{2-6} alkenyl, C_{2-6}alkynyl each being optionally substituted with one or more halogen, OH, oxo, CN, C_{1-3}alkoxy, $NR_{10}R_{11}$, $NR_{10}COR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy, arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl or heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two OH, oxo or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$ and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

m is 1-4, n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

In another embodiment of the invention there are provided compounds of the formula (Ia) as described immediately above, and wherein:

X is NH or N-CH_3;

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl; and wherein R_a is attached at the 4- position;

R_1 and R_2 are the same or different and selected from: halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is methyl or C_{2-4} alkenyl each being optionally substituted with one or more OH, CN, $NR_{10}R_{11}$, $CONR_{10}R_{11}$ or CO_2R_{12};
or R_9 is heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy or OH;

R_{12} is H or C_{1-3}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

In still a further embodiment of the invention there are provided compounds of the formula (Ia) as described immediately above, and wherein:

R_a is H or hydroxymethyl;

R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

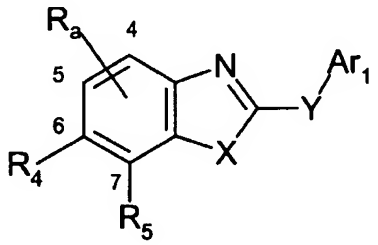
R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;
or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino.

In another aspect of the invention, there are provided intermediate compounds of the formula(III) useful in the synthetic schemes and examples set forth below. In yet another aspect of the invention are particular intermediate compounds of the formula(III), (representative examples shown Table 1 below) which possess physiological activity.

In their broadest generic aspect, intermediate compounds described above are represented by the formula (III):



(III)

wherein:

Ar_1 is an aromatic or nonaromatic carbocycle, heteroaryl or heterocycle; wherein said carbocycle, heteroaryl or heterocycle is optionally substituted by one or more R_1, R_2 and R_3;

X is NH, N-C_{1-3}alkyl, N,cyclopropyl, S or O;

Y is NR_{15}, S or O;

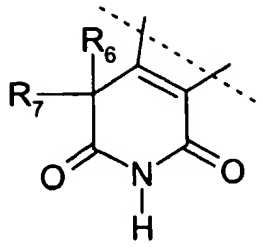
R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl;

wherein each R_a is independently optionally substituted with one or more C_{1-3}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5-position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formula C:



C

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$ and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with alkoxy, OH or phenyl;

or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$; and

m is 1-4, n is 0-3 and p is 0-2.

One embodiment of the compounds of formula(III) are those wherein:

Ar_1 is

a) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl;

b) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cycloheptenyl;

c) phenyl, naphthyl; indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl;

d) heteroaryl selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, benzothiazolyl, quinazolinyl, and indazolyl, or a fused heteroaryl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole,

cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; or

e) a heterocycle selected from: pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl and indolinyl;

wherein each of the above Ar_1 are optionally substituted by one or more R_1, R_2 and R_3 as hereinabove defined;

R_a is H, C_{1-6}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, phenyl or heteroaryl selected from: pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, pyrazolyl, imidazolyl, furyl, thiazolyl and thienyl; each R_a being optionally substituted with one or more phenyl, halogen, C_{1-3}alkyl, C_{1-3} alkoxy, OH, oxo, or $NR_{10}R_{11}$; wherein R_a is at the 4- position;

R_3 is H, halogen, methyl, methoxy, hydroxymethyl or OH;

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, benzyl and phenyl; wherein said alkyl, cycloalkyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H or C_{1-6}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;

and

or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

Another embodiment of the compounds of the formula(III) are those described immediately above, and wherein:

Ar_1 is phenyl, or pyridyl;

X is NH or N-CH_3;

Y is NH and

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl;

R_1 and R_2 are the same or different and selected from: halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl are optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy or OH;

R_{12} is H or C_{1-3}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

In yet another embodiment of the compounds of formula(III) are those described immediately above, and wherein:

Ar_1 is phenyl;

R_a is H or hydroxymethyl;

R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;
or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino.

In a further embodiment of the invention, there are provided the following compounds of the fomulas (I) and (Ia):

2-(2,6-Dichlorophenylamino)-6,7-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-3,5-dihydro-imidazo[4,5-i]phenanthridin-4-one;

2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-7-methyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino) -1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-6-acetic acid ethyl ester;

3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-acrylic acid methyl ester;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-hydroxyethyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-6- carboxylic acid methyl ester;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-acrylic acid methyl ester;

3-[2-(2,6-Dichlorophenylamino) -1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-6-yl]propionic acid ethyl ester

N-Benzyl-*N*-methyl-2-[(2,6-dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-6-yl] acetamide;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-morpholin-4-ylethyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2-Chloro-6-methylphenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(4-Bromo-2-dichlorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-N-methoxy-N-methylacrylamide;

2-(2-Chloro-6-nitrophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

N-Benzyl-3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-acrylamide;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-acrylic acid 4-morpholine amide;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl -6-[3-(4-morpholino)propyl]-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-4-hydroxymethyl-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dimethylphenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2-Ethyl-6-methylphenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(3-phenylaminopropyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino-6-{3-[4-(2-diethylaminoethoxy)-phenylamino]propyl}-1,7-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2-Bromo-6-chloro-4-fluorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-4-(2-hydroxyethylaminomethyl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-4-(4-methoxybenzylaminomethyl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-vinyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-4-(2,6-difluoropyridin-3yl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-4-(3-methylphenyl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-6- carboxylic acid 2-(4-moropholino)ethyl ester;

2-(2,6-Dichlorophenylamino)-4-(3-hydroxy-2-oxo-propyl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

N-4-(2-Diethylaminoethoxy)phenyl-3-[2-(2,6-dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-acrylamide;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-N-methyl acrylamide;

9- Hydroxy-2-(2,6-dichlorophenylamino)-3,5,6,7,8,9-hexahydro-imidazo[4,5-i]phenanthridin-4-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-hydroxypropen-1-yl)-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(2-phenylethenyl)-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2-Amino-6-chlorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-4-vinyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-4-(3-methoxypropyn-1-yl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-4-(5-phenylpent-1-ynyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-vinyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-morpholin-4-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-[2-(2-hydroxyethyl)aminoethyl]-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

3-[2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-*h*]isoquinolin-7-yl]-acrylonitrile;

2-(2-Chloro-6-methylphenylamino)-1,7-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(3-hydroxypropyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2-Chloro-6-methylphenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

7-(3-Aminopropen-1-yl)-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-pyrrolidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

7-(3-Benzylmethylaminopropen-1-yl)2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichloro-4-methoxyphenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichloro-4-methoxyphenylamino)-1,6-dimethyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dimethylphenylamino)-1,7-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(4-methylpiperazin-1-yl-propen-1-yl)-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-piperidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-{3-[ethyl(2-hydroxyethyl)amino]propen-1-yl}-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(3-hydroxypyrrolidin-1-yl)-propen-1-yl]- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

7-(3-Dibutylaminopropen-1-yl)-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-{3-[(2-methoxyethyl)methylamino]propen-1-yl}-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

7-(3-Diethylaminopropen-1-yl)-1,6-dimethyl-2-(2,6-dimethylphenylamino)-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-{3-[(2-diethylaminoethyl)methylamino]-propen-1-yl}-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

7-(3-Diethylaminopropen-1-yl)-1,6-dimethyl-2-(2,4,6-trichlorophenylamino)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-6-methyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(2-pyrrolidin-1-ylmethylpyrrolidin-1-yl)-propen-1-yl]-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

7-[3-(2*S*-Aminomethylpyrrolidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

1-{3-[2-(2,6-Ddichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-*L*-proline carboxamide

1-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-3-carboxamide

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(methylhydrazonomethyl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

7-[3-(3-Aminopyrrolidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(3-acetamidopyrrolidin-1-yl)-propen-1-yl]- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(3-dimethylaminopyrrolidin-1-yl)-propen-1-yl]- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

1-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-2-carboxamide

7-[3-(3-Aminomethylpiperidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

1-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-3-carboxylic acid diethylamide

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-ethynyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

1-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-3-methyl urea

Cyclohexane carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

2-(2,6-Dichlorophenylamino)-1-methyl-7-phenyl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl} methanesulfonamide

3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl urea

1-Cyclohexyl-3-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-urea

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl} benzenesulfonamide

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-ethylaminopropen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-guanidine

Piperidine-3-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

L-Proline {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

D-Proline {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-benzamide

L-Azetidine-2-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

Piperidine-2-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide; and

the pharmacuetically acceptable derivatives thereof.

In yet still a further embodiment of the invention, there are provided the following compounds of the fomulas (I) and (Ia):

2-(2,6-Dichlorophenylamino)-3,5-dihydro-imidazo[4,5-i]phenanthridin-4-one;

2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-hydroxyethyl)-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-h]isoquinoline-6- carboxylic acid methyl ester;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylic acid methyl ester;

2-(2-Chloro-6-methylphenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-N-methoxy-N-methylacrylamide;

2-(2-Chloro-6-nitrophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

N-Benzyl-3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylamide;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylic acid 4-morpholine amide;

2-(2,6-Dichlorophenylamino)-4-hydroxymethyl-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-vinyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-h]isoquinoline-6- carboxylic acid 2-(4-moropholino)ethyl ester;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-hydroxypropen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-vinyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-morpholin-4-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

3-[2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylonitrile;

2-(2-Chloro-6-methylphenylamino)-1,7-dimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2-Chloro-6-methylphenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-pyrrolidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(4-methylpiperazin-1-yl-propen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-piperidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-{3-[ethyl(2-hydroxyethyl)amino]propen-1-yl}-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

7-(3-Diethylaminopropen-1-yl)-1,6-dimethyl-2-(2,6-dimethylphenylamino)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-{3-[(2-diethylaminoethyl)methylamino]-propen-1-yl}-1,6-dimethyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

7-(3-Diethylaminopropen-1-yl)-1,6-dimethyl-2-(2,4,6-trichlorophenylamino)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-6-methyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(2-pyrrolidin-1-ylmethylpyrrolidin-1-yl)-propen-1-yl]-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

7-[3-(2*S*-Aminomethylpyrrolidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

1-{3-[2-(2,6-Ddichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-*L*-proline carboxamide

1-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-3-carboxamide

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(methylhydrazonomethyl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

7-[3-(3-Aminopyrrolidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(3-acetamidopyrrolidin-1-yl)-propen-1-yl]- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(3-dimethylaminopyrrolidin-1-yl)-propen-1-yl]- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

1-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-2-carboxamide

7-[3-(3-Aminomethylpiperidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one

1-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-3-carboxylic acid diethylamide

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-ethynyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

1-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-3-methyl urea

Cyclohexane carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

2-(2,6-Dichlorophenylamino)-1-methyl-7-phenyl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl} methanesulfonamide

3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl urea

1-Cyclohexyl-3-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-urea

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl} benzenesulfonamide

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-ethylaminopropen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-guanidine

Piperidine-3-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

L-Proline {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

D-Proline {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-benzamide

L-Azetidine-2-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide

Piperidine-2-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide; and

the pharmacuetically acceptable derivatives thereof.

Any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of the invention can exist in more than one tautomeric form. The invention includes all such tautomers.

The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the invention.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C_{1-6}alkoxy" is a C_{1-6}alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, pentoxy and hexoxy. All alkyl, alkylene or alkynyl groups shall be understood as being branched or unbranched unless otherwise specified. Other more specific definitions are as follows:

The term "halogen" as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine.

The term "heteroaryl" refers to a stable 5-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic aromatic heterocycle radical. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Example "heteroaryl" radicals include, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, quinolinyl,

isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, benzothiazolyl, quinazolinyl, 2,4-dioxo-quinazolinyl, imidazo[4,5-*c*]pyridinyl and indazolyl, or a fused heteroaryl such as cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene;

The term "heterocycle" refers to a stable 4-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated, and is non-aromatic. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Example "heterocycle" radicals include azetidinyl, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl,indolinyl, 2,3-dihydrobenzimidazolyl and 2,3-dihydro-1*H*-imidazo[4,5-*c*] pyridinyl. As used herein and throughout this specification, the terms "nitrogen" and "sulfur" and their respective elements symbols include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.

The term "aryl" shall be understood to mean a 6-10 membered aromatic carbocycle, "aryl" includes, for example, phenyl and naphthyl; other terms comprising "aryl" will have the same definition for the aryl component, examples of these moieties include: arylalkyl, aryloxy or arylthio.

The term "carbocycle" shall be understood to mean a 3-10 membered aromatic or nonaromatic cyclic carbon chain. Examples of nonaromatic carbocycles include

cyclopropyl, cyclobutyl, cyclopentyl and the like. Examples of aromatic carbocycles include the "aryl" compounds as described hereinabove.

The term "acyl" shall be understood to mean an R-(C=O)- moiety wherein R is an alkyl. Examples of R can be a C_{1-10}alkyl, saturated or unsaturated, branched or unbranched, or R can be "aryl" as defined hereinabove. "Acyloxy" shall be understood to mean an R-CO_2- group wherein R is as defined in this paragraph.

The invention includes pharmaceutically acceptable derivatives of compounds of the invention. A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, a pharmacologically active metabolite or pharmacologically active residue thereof.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of this invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-(C_1-C_4 alkyl)$_4^+$ salts.

In addition, the compounds of this invention include prodrugs of compounds of the invention. Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce a compound of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction, enzymatically, metabolically or otherwise.

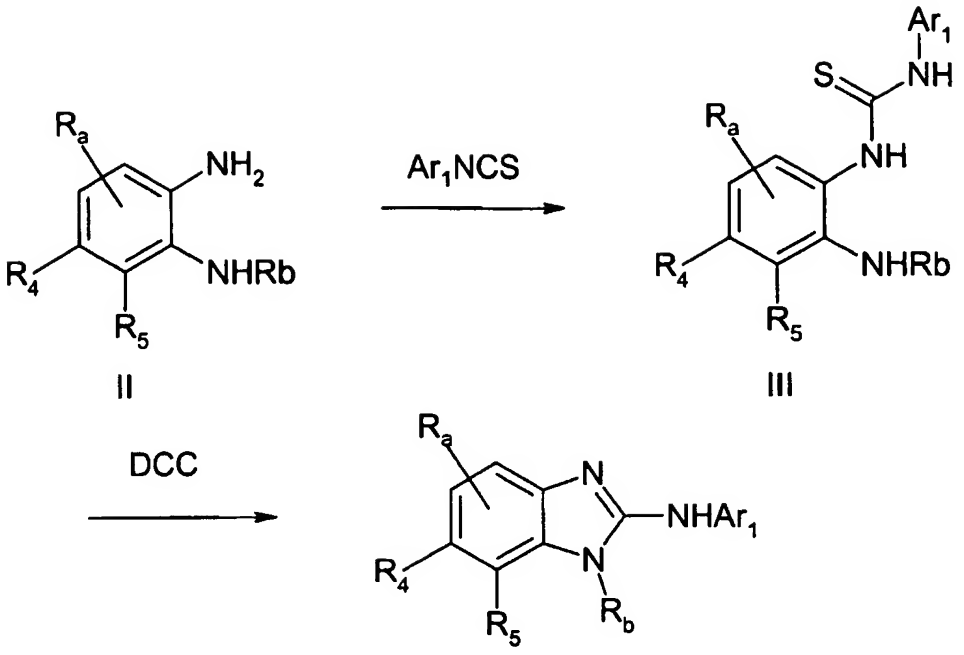
Specifically, when a prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound of the invention, thereby imparting the desired pharmacological effect.

General Synthetic Methods

The compounds of the invention may be prepared by the methods described below. Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitered by thin layer chromatography (TLC) if desired. If desired, intermediates and products may be purified by chromatography on silica gel and/or recrystallization. Starting materials and reagents are either commercially available or may be prepared by one skilled in the art using methods described in the chemical literature.

A general procedure (Method A) that may be used to synthesize compounds of formula (I) is illustrated in Scheme I.

Scheme I (Method A)

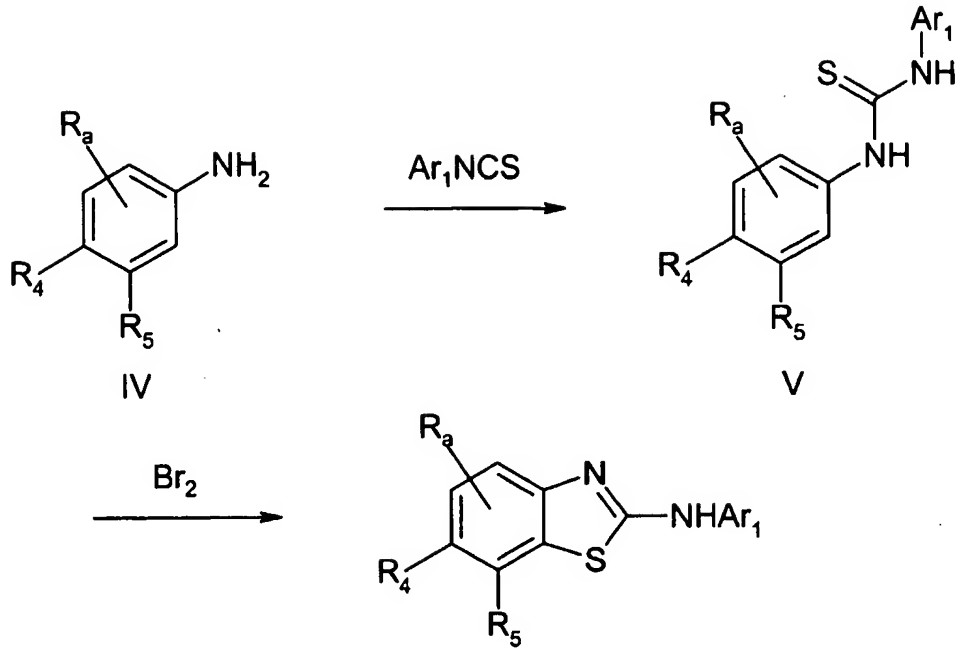


I (NR_b = X; R_b = H or C_{1-3} alkyl; Y = NH) or a precursor to I

An optionally substituted diamine II is reacted with an aryl isothiocyanate in a suitable solvent such as EtOAc, DMF or THF at about ambient to reflux temperature for about 3 to 24 hr to provide thiourea III. Alternately, one can begin with a salt of II and react with an aryl isothiocyanate in pyridine or in a neutral solvent such as THF in the presence of a suitable base such as triethylamine. Reaction of the thiourea with a suitable activating agent such as 1,3-dicyclohexylcarbodiimide (DCC) or mercuric oxide in a suitable solvent such as THF or DMF at about ambient to reflux temperature provides I or a precursor to I which may undergo further chemical transformation to obtain the desired compound. If desired, one may perform the two steps without isolating the thiourea, by adding DCC or mercuric oxide to the reaction of II and the aryl isothiocyanate.

One may also prepare benzothiazoles (formula I, X = S) by Method A, starting with the analogous aminothiophenol. Preferably, one may also use Method B illustrated in Scheme II and described below.

Scheme II (Method B)



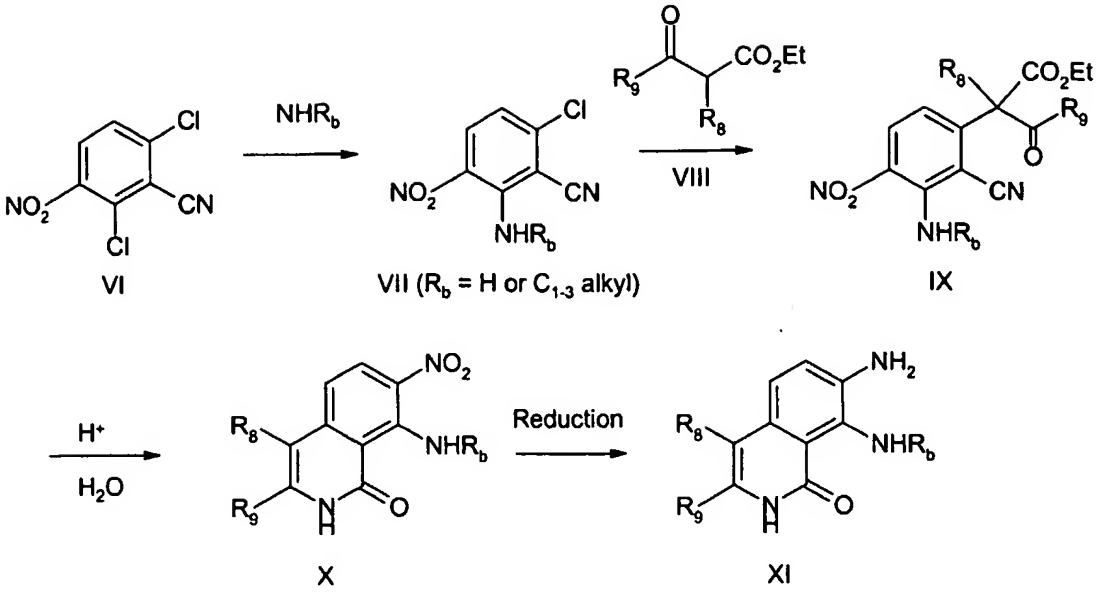
I (X = S; Y = NH) or a precursor to I

In this method, an appropriately substituted aniline is reacted with an aryl isothiocyanate as in Method A to provide thiourea V. Reaction of V under cyclizing conditions, such as in the presence of bromine in a suitable solvent such as chloroform at about reflux temperature, provides I (X = S) or a precursor to I.

The starting diamine (II) in Method A may be prepared by reduction of a nitroaniline, for example under hydrogen atmosphere in the presence of a suitable catalyst such as palladium on carbon in a suitable solvent, such as EtOAc or HOAc.

One procedure (Method C) for preparing starting nitroanilines is illustrated in Scheme III and described below.

Scheme III (Method C)

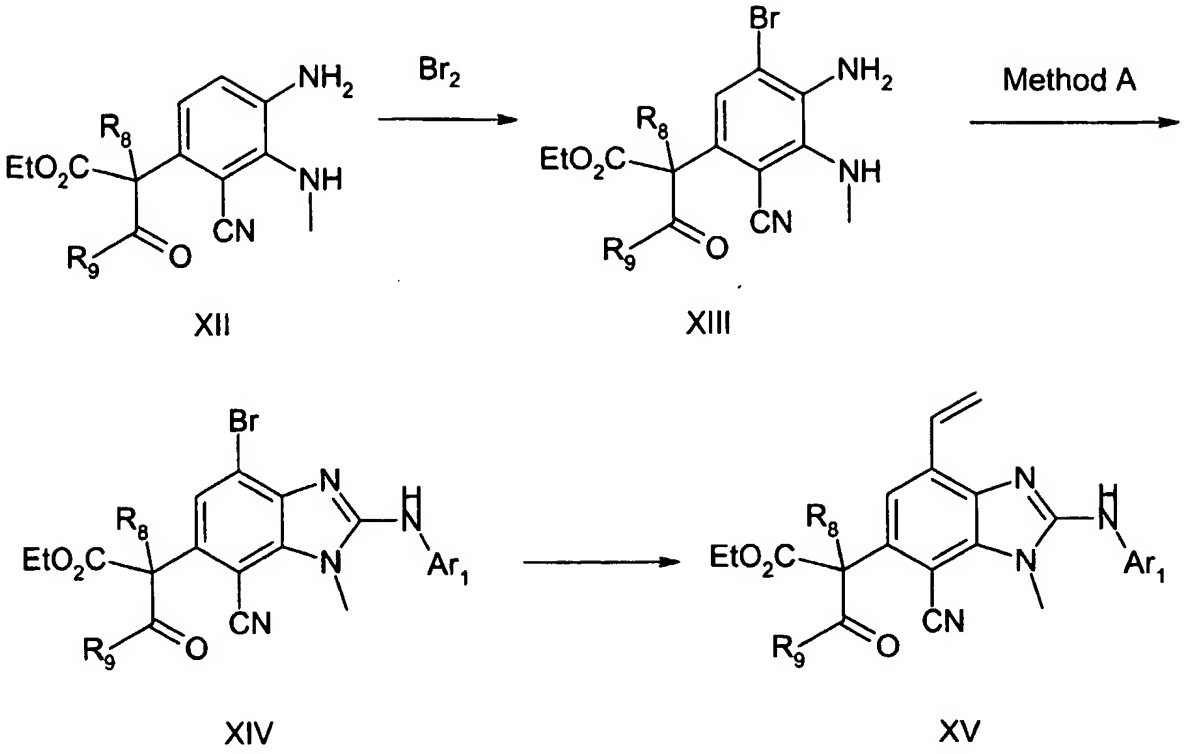


In Method C, 2,6-dichloro-3-nitrobenzonitrile (VI) is reacted with an amine in a suitable solvent, such as EtOH, THF or EtOAc, optionally in a pressure flask and at about 0 to 80 ^{o}C, to provide VII. Reaction of VII with keto-ester VIII in the presence of a suitable base, such as K_2CO_3, potassium *t*-butoxide or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a suitable solvent, such as DMF or DMSO at about ambient temperature provides IX. Hydrolysis and cyclization of IX to provide X is accomplished by reaction with aqueous acid, for example a mixture of acetic acid, sulfuric acid and water at about reflux temperature. Reduction of nitroaniline X, in a suitable solvent, preferably acetic acid and/or trifluoroacetic acid, as described above, provides XI.

In a variation of Method C, one may reduce intermediate IX as described above, to the corresponding diamine and form the benzimidazole by Method A prior to formation of the isoquinolinone.

A procedure for introducing R_A into compounds of formula (I) is illustrated in Scheme IV.

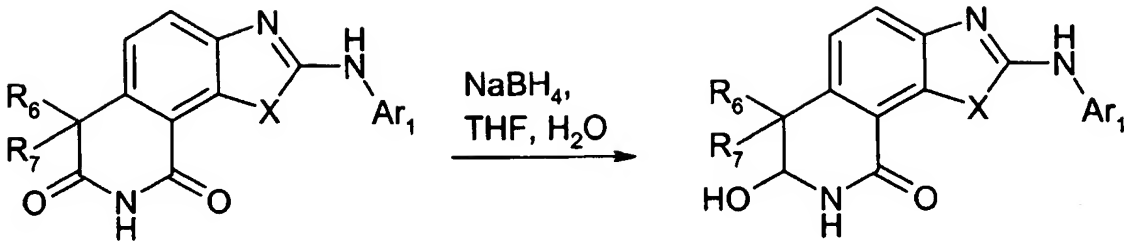
Scheme IV



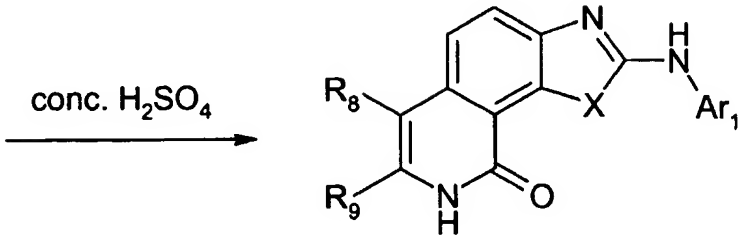
Intermediate XII (prepared as described in Scheme III for preparation of IX, followed by reduction) is reacted with bromine in a suitable solvent, such as chloroform at ambient temperature to provide XIII. Intermediate XIII is converted to XIV according to Method A. Cross-coupling chemistry can be used to introduce carbon in place of bromine. For example, reaction with vinyl tributyltin in the presence of a suitable catalyst, such as $(PPh_3)_2PdCl_2$, in a suitable solvent, such as 1-methyl-2-pyrrolidinone (NMP) at about 100 ^oC, provides XV. Alternately, reaction with a terminal alkyne in the presence of a suitable catalyst, such as $(PPh_3)_2PdCl_2$, and CuI, and a suitable base, such as triethylamine in a solvent such as THF at about ambient temperature provides an alkyne as R_a. Other R_a may be obtained by transformation of these R_a by methods known to those skilled in the art. Several of these transformations are exemplified below.

A method for preparing compounds of the invention in which R_4 and R_5 represent ring B, which is based on the procedure described in *J. Heterocyclic Chem.*, **1970**, *7*, 615, is shown in Scheme V.

Scheme V



XVI XVII



XVIII

Intermediate XVI (prepared according to Method A or Method B) is reacted with a reducing agent such as sodium borohydride, in a suitable solvent, such as THF or dioxane, at about 0°C to ambient temperature, to give intermediate XVII, in which one carbonyl of the imide has been reduced selectively. Treatment of XVII with a strong acid, such as sulfuric acid, at ambient temperature, causes rearrangement to the isoquinolone XVIII. It will be appreciated that this method is most suitable for compounds where R_6, R_7, R_8 and R_9 are all the same group, preferably methyl. In a variation of this method, the reduction of the imide and rearrangement to the isoquinolone can be carried out prior to forming the benzimidazole ring.

Functional groups at R_8 or R_9 on compounds of formula (I) or intermediates prepared as illustrated in the Schemes above may also be transformed by methods known to those skilled in the art to prepare additional compounds of the invention. Several of these transformations are also exemplified below.

Methods of Therapeutic Use

The compounds of the invention are useful in inhibiting the activity of src-family kinases and PDGFR kinase. In doing so, the compounds are effective in blocking disease processes mediated by these kinases. For example, by inhibiting p56 lck, the compounds block downstream signaling events following T cell activation by antigen. Activation of antigen-specific T cells is necessary for the induction and progression of diseases, including autoimmune diseases, allergic diseases and transplant rejection (J.H. Hanke et al., *Inflamm. Res.*, 1995, *44*, 357). Therefore the compounds of the invention are useful for treating such diseases. These include but are not limited to rheumatoid arthritis, multiple sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, systemic lupus erythematosus, insulin-dependent diabetes mellitus and asthma.

In view of their inhibitory effect on src-family kinases and PDGFR kinase, the compounds of the invention are useful in treating cancer. For example, the compounds of the invention are useful in treating src-dependent tumors, such as in mammary carcinoma, colon carcinoma, melanoma and sarcoma, and are also useful in treating PDGF-dependent tumors, such as ovarian cancer, prostate cancer and glioblastoma.

By inhibiting p60src, compounds of the invention may also be useful in treating osteoporosis, Paget's disease, bone inflammation and joint inflammation . By inhibiting PDGFR kinase, compounds of the invention may also be useful in treating fibrotic diseases, restenosis and atherosclerosis. By inhibiting lyn kinase, the compounds of the invention may also be useful in enhancing or potentiating the effectiveness of radiation therapy.

For therapeutic use, the compounds of the invention may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, rectally, topically or by inhalation. The

preferred modes of administration are oral and intravenous. Compositions comprising the compounds of the invention for each of the aforementioned routes of administration will be apparent to the skilled artisan. For example, one embodiment of the invention provides for pharmaceutical compositions including a pharmaceutically effective amount of the compounds according to the invention. Such pharmaceutical compositions will include pharmaceutically acceptable carriers and adjuvants as further described below.

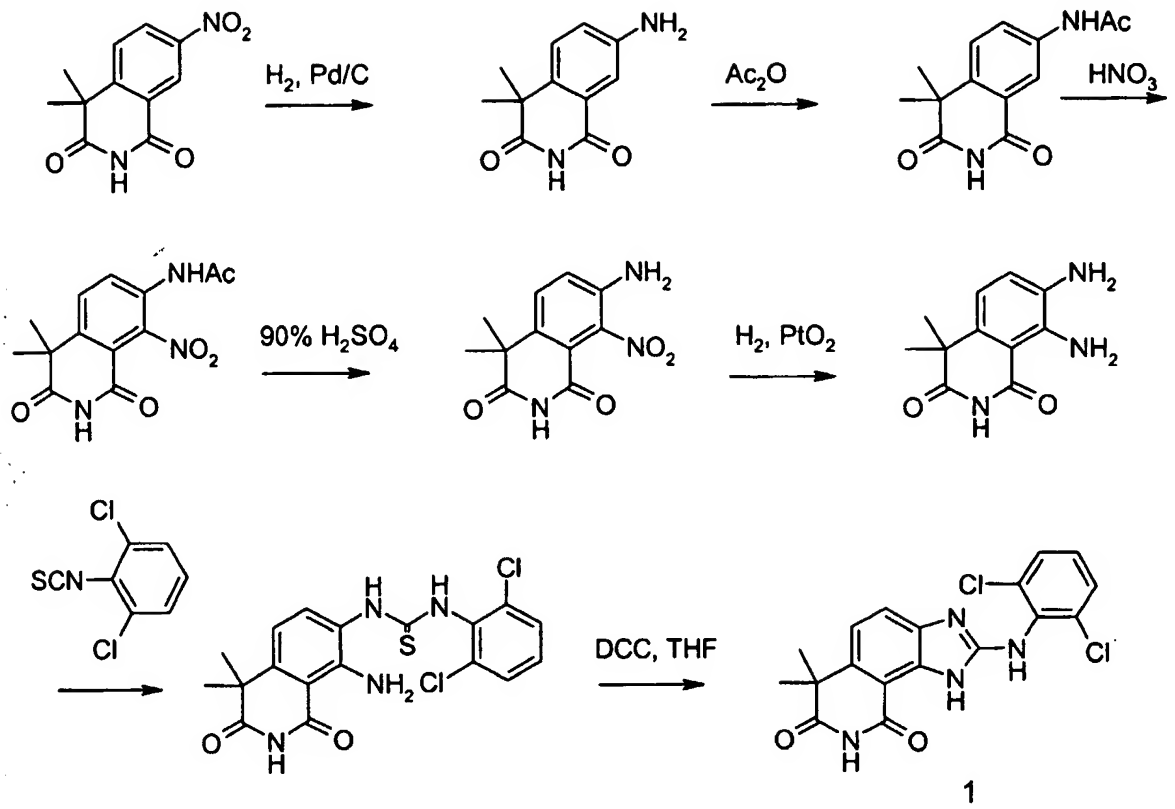
The compounds of this invention may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutic compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 5%, but more preferably at least about 20%, of a compound of formula (I) (w/w) or a combination thereof. The optimum percentage (w/w) of a compound of formula(I) may vary and is within the purview of those skilled in the art. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

As mentioned above, dosage forms of the compounds of this invention include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule,

suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 1-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

SYNTHETIC EXAMPLES

Example 1: Synthesis of 2-(2,6-Dichlorophenylamino)-6,6-dimethyl-1*H*,6*H*-imidazo[4,5-*h*]isoquinoline-7,9-dione.



4,4-Dimethyl-7-nitro-2*H*,4*H*-isoquinoline-1,3-dione, prepared as described in US 4666923 (1987), (1.0g, 4.5mmol) in methanol (50mL) was hydrogenated over 10% Pd/C (30mg) at 50psi for 1.5h. The catalyst was removed by filtration and the solvent removed to give 8-amino-4,4-dimethyl-2*H*,4*H*-isoquinoline-1,3-dione (0.90g, 98%).

The above amine (1.5g, 7.35mmol) was stirred in acetic anhydride (9mL) at room temperature for 3h, then poured on to ice. The precipitate was filtered, washed with water and dried to give 7-acetamido-4,4-dimethyl-2*H*,4*H*-isoquinoline-1,3-dione (1.55g, 86%)

The above amide was converted to 7-acetamido-4,4-dimethyl-8-nitro-2*H*,4*H*-isoquinoline-1,3-dione as described in US 4176184 (1979).

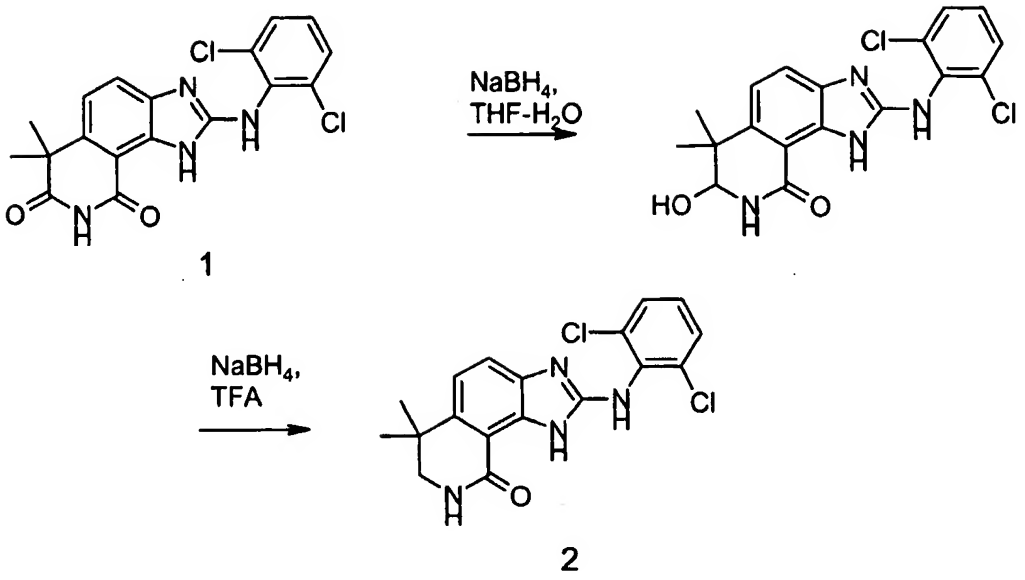
7-Acetamido-4,4-dimethyl-8-nitro-2*H*,4*H*-isoquinoline-1,3-dione (4.0g, 13.7mmol) was added to 90% H_2SO_4 and heated at 70°C for 8h. The cooled mixture was poured onto

ice. The precipitate was collected, dissolved in ethyl acetate, washed with water, dried and evaporated to give 7-amino-4,4-dimethyl-8-nitro-2*H*,4*H*-isoquinoline-1,3-dione (3.38g, 99%), mp 259-263°C; MS (CI) 250 (MH+).

A solution of the above amine (1.5g, 6.0mmol) in methanol (50mL) was hydrogenated over platinum oxide (30mg) at 50 psi for 1.25h. The mixture was filtered through diatomaceous earth and evaporated to provide 7,8-diamino-4,4-dimethyl-2*H*,4*H*-isoquinoline-1,3-dione. (1.31g, 100%). MS (CI) 220 (MH+).

As described in Method A, 2,6-dichlorophenylisothiocyanate (1.16g, 5.7mmol) was added to a suspension of 7,8-diamino-4,4-dimethyl-2*H*,4*H*-isoquinoline-1,3-dione (1.31g, 6.0mmol) in ethyl acetate (40mL) and the mixture stirred overnight. The solid was filtered and dried to yield the thiourea (1.55g, 61%). mp >300°C; MS (CI) 423, 425 (MH+). A solution of the thiourea (2.23g, 5.28mmol) in THF (50mL) and dicyclohexylcarbodiimide (1.11g, 5.4mmol) was heated under reflux with stirring for 4h. The cooled solution was stirred overnight, filtered, and the crystals washed with CH_2Cl_2 to give the title compound (1.20g). The filtrate was evaporated and triturated with CH_2Cl_2 to give more product (0.7g, 93% combined yield), mp 290-292°C; MS (EI) 388, 390 (M+).

Example 2: Synthesis of 2-(2,6-Dichlorophenylamino)-6,6-dimethyl-7,8-dihydro-1*H*,6*H*-imidazo[4,5-*h*]isoquinoline-9-one.

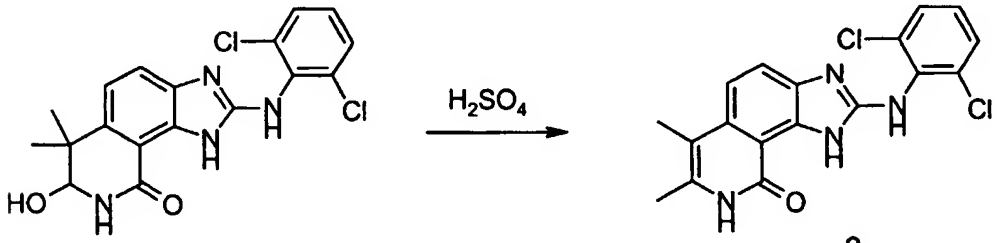


To a solution of the product of Example 1 (90mg, .23mmol) in THF (5mL) was added $NaBH_4$ (90mg, 2.3mmol) followed by water (4 drops). The reaction mixture was stirred at ambient temperature for 1 h. Subsequently, 1N HCl (5mL) was added dropwise and the reaction mixture was stirred an additional 15 minutes, neutralized with $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine, dried and evaporated yielding the alcohol 2-(2,6-dichlorophenylamino)-6,6-dimethyl-7-hydroxy-7,8-dihydro-1*H*,6*H*-imidazo[4,5-*h*]isoquinoline-9-one (90mg 99%). This intermediate was used immediately due to its instability. It was characterized as the methyl ether, which was prepared by dissolving the product in MeOH/HCl and stirring for several hours. After evaporation, the residue was partitioned between EtOAc/aq $NaHCO_3$. The organic phase was washed with brine, dried and evaporated to the methyl ether derivative, mp 278-280°C(dec); MS (ES) 405 (MH+).

The alcohol from above (100mg, .26mmol) was dissolved in TFA (2 mL) and this solution was subsequently added to a solution of sodium tristrifluoroacetoxyborohydride (generated in-situ from 160mg, 4.2mmol of sodium borohydride and 3mL TFA) at 0°C. The reaction mixture was stirred at ambient temperature for 4h, the solvent was evaporated, the residue was triturated with water and the resultant mixture was neutralized with $NaHCO_3$ and filtered yielding the title compound (85mg, 92%). This

product was purified by flash chromatography on SiO_2 using 4% $MeOH/CH_2Cl_2$ as eluant and recrystallization from EtOAc, mp 287-290°C; MS (CI) 375 (MH^+).

Example 3a : Synthesis of 2-(2,6-Dichlorophenylamino)-6,7-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.



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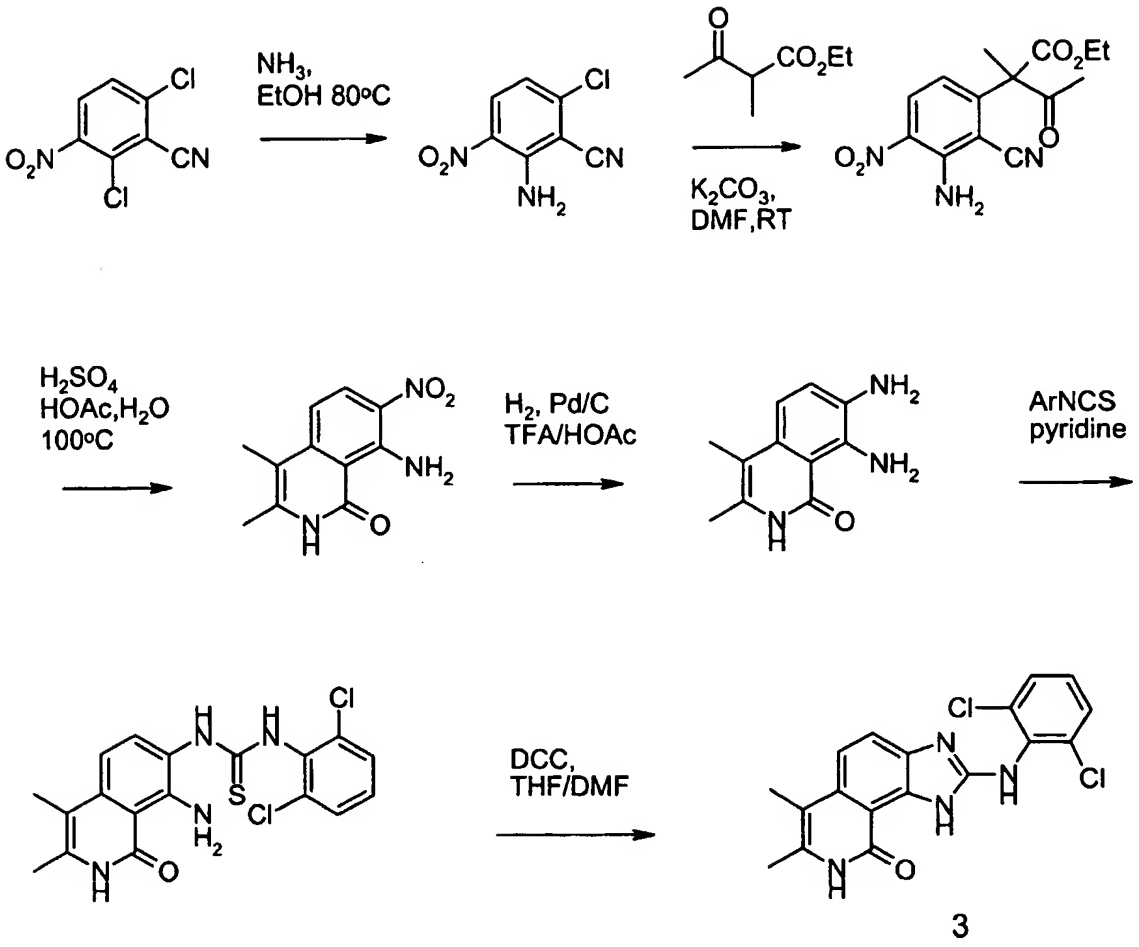
2-(2,6-Dichlorophenylamino)-6,6-dimethyl-7-hydroxy-7,8-dihydro-1*H*,6*H*-imidazo[4,5-*h*]isoquinoline-9-one (from Example 2) (45mg, 0.11mmol) was suspended in conc. H_2SO_4 (1mL) and the resultant mixture was stirred at ambient temperature for 15 min. The solution was poured over ice, neutralized with $NaHCO_3$ and filtered. The filtrate was triturated with water (10mL) and centrifuged. The liquid was decanted, and the residual solid was triturated with methanol and centrifuged. The supernatant was decanted and the residue dried to give the title compound (35mg, 84%). Mp >300°C; MS (ES) 373 (MH^+).

Example 3b: Synthesis of 2-(2,6-Dichlorophenylamino)-6,7-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one (Method C).



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A 500mL pressure flask was charged with 2,6-dichloro-3-nitrobenzonitrile (30.0g, 138mmol) and a 5.1M solution of ammonia in EtOH (170mL). The flask was sealed and heated in an oil bath at 80°C with stirring for 1.5h. The cooled solution was filtered, the crystals washed with water and dried to yield 2-amino-6-chloro-3-nitrobenzonitrile (18.4g, 68%), mp 181-184°C; MS (ES^-) 196, 198 ($M-H^-$).

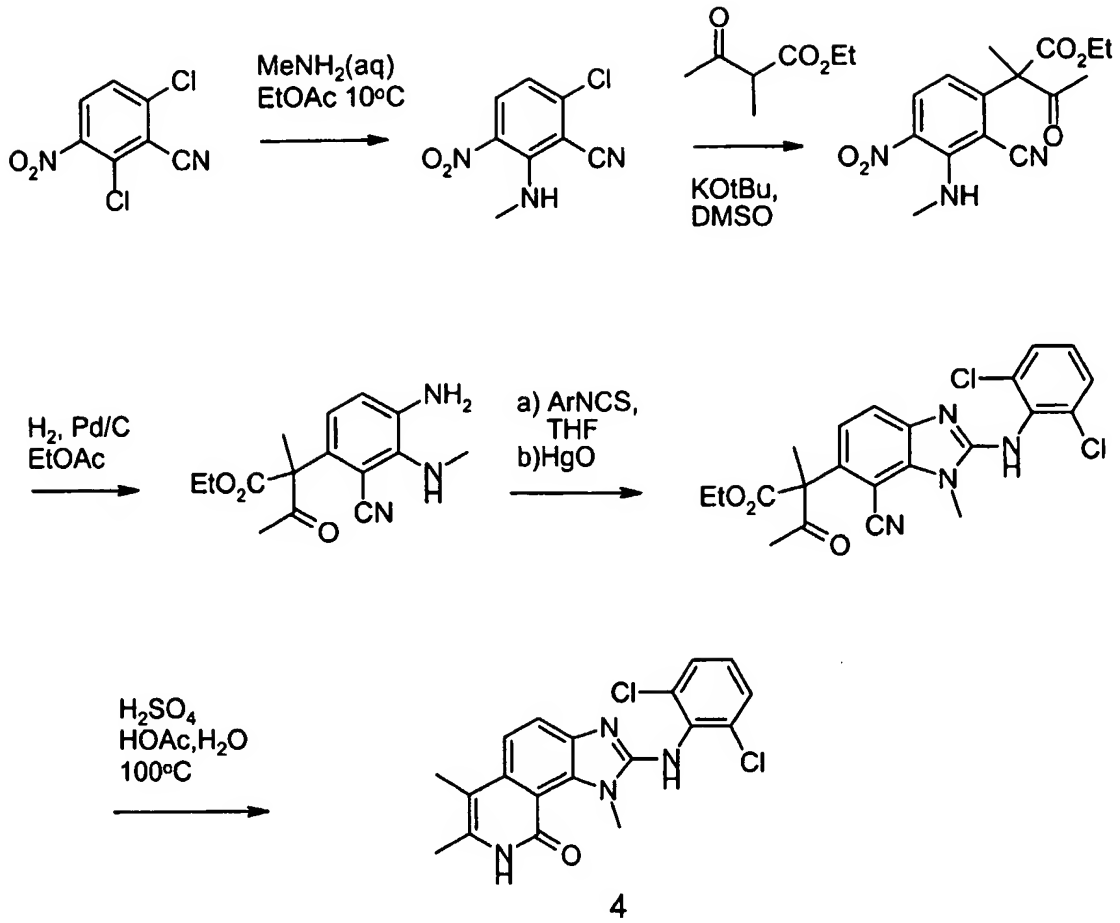
To a solution of 2-amino-6-chloro-3-nitrobenzonitrile (1.97g, 10mmol) and ethyl 2-methylacetoacetate (3.6g, 25mmol) in DMF (10mL) was added finely powdered K_2CO_3, and the mixture stirred vigorously for 24h. The deep red mixture was diluted with EtOAc and washed in turn with 2M HCl, water and brine. The residue after evaporation was purified by flash chromatography in hexane/EtOAc 3:1 to yield 2-(3-amino-2-cyano-4-nitrophenyl)-2-methyl-3-oxobutyric acid ethyl ester as an oil (1.39g, 46%), MS (NH_3 CI) 323 ($M+NH_4^+$), 293 ($M+NH_4-NO^+$).

The ester from above (1.39g, 4.56mmol) was added to a mixture of acetic acid (20mL), H_2SO_4 (3mL) and water (2mL), and the solution heated at 100°C for 3h. The cooled solution was diluted with water (30mL), the precipitate was collected, washed with water and MeOH and dried to give 8-amino-3,4-dimethyl-7-nitro-2*H*-isoquinolin-1-one (0.76g, 72%). mp >300°C.

A solution of the amino isoquinolin-1-one from above (0.20g, 0.86mmol) in trifluoroacetic acid (11mL) and acetic acid (7mL) was hydrogenated over 10% palladium on carbon (21mg) at 50psi for 2h. The solution was filtered through diatomaceous earth, washing with acetic acid, and the filtrate evaporated to give 7,8-diamino-3,4-dimethyl-2*H*-isoquinolin-1-one ditrifluoroacetate salt (310mg, 83%).

A suspension of the diamino isoquinolin-1-one ditrifluoroacetate salt from above (1.15g, 2.67mmol) and 2,6-dichlorophenylisothiocyanate (0.60g, 2.93mmol) in pyridine (16mL) was stirred for 18h at room temperature (Method A). The solution was diluted with toluene and evaporated, and remaining pyridine removed with a toluene azeotrope. The residue was triturated with EtOAc to give the thiourea (1.17g). A portion of this material (0.50g, 1.23mmol) and dicyclohexylcarbodiimide (0.375g, 1.84mmol) were heated together in DMF under argon at 80°C for 4h. The cooled solution was evaporated and triturated first with cold MeOH, then with boiling MeOH, to leave the title compound as a light tan solid, (0.309g, 73%), identical with the sample obtained in Example 3a.

Example 4: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.



4

A solution of 2,6-dichloro-3-nitrobenzonitrile (98.7g, 0.455mol) in EtOAc (910mL) was cooled to 5°C. 40% Aqueous methylamine (79.5mL, 1.14mol) was added with vigorous mechanical stirring, keeping the temperature at 10-15°C. After addition was complete, stirring was continued for 3h at the same temperature. More methylamine (16mL, 0.23mol) was added, and the mixture stirred for a further 1.5h at room temperature. Water (300mL) was added, followed by hexane (450mL). The mixture was stirred for 15min, filtered, and the solid washed with water and MeOH, to give 6-chloro-2-methylamino-3-nitrobenzonitrile (80.3g, 83%), mp 167-170°C.

To a stirred solution of potassium t-butoxide (24.3g, 206mmol) in DMSO (500mL) was added ethyl 2-methylacetoacetate (34.3g, 233mmol), dropwise over 5min. The temperature rose to 30°C. 6-Chloro-2-methylamino-3-nitrobenzonitrile (43.6g, 190mmol) was added in portions over 15min. The temperature rose to 40°C. The

solution was stirred for 1h with no external heating or cooling. The mixture was poured into 10% NH_4Cl (500mL), and extracted with EtOAc (2 x 500mL). The combined extracts were washed with water (2 x 250mL) and brine, and evaporated. MeOH (200mL) was added to the residue and stirred for 1.5h. The yellow solid was filtered, washed with cold MeOH (25mL) and dried to give 2-(2-cyano-3-methylamino-4-nitrophenyl)-2-methyl-3-oxobutyric acid ethyl ester (36.2g, 60%), mp 87-91°C.

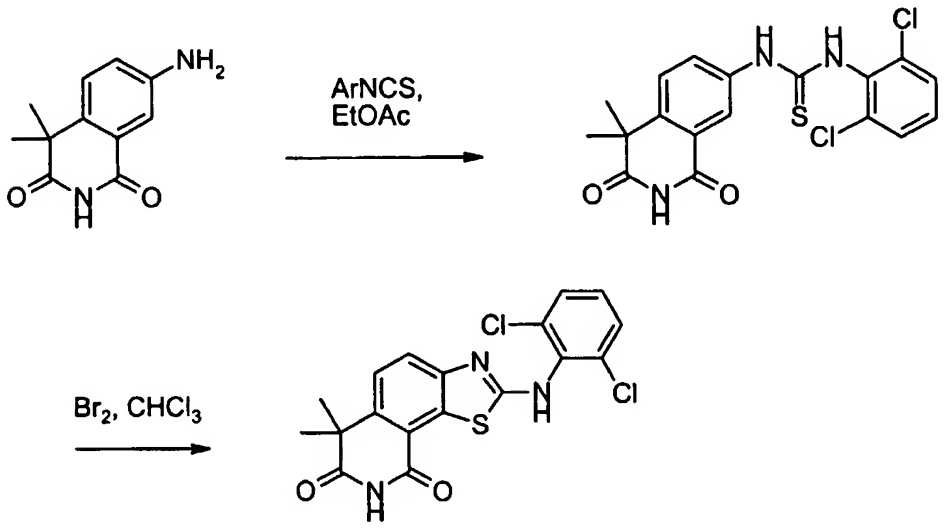
A solution of the above ester (10.5g, 32.5mmol) in EtOAc (130mL) was hydrogenated over 10% palladium on carbon (0.5g) at 50psi for 24h. The catalyst was removed by filtration through diatomaceous earth, and the filtrate was evaporated. A mixture of EtOAc/hexane (1:1, 10mL) was added to the residue and the resulting mixture was stirred for 0.5h. The crystals were filtered and washed with hexane to give 2-(4-amino-2-cyano-3-methylaminophenyl)-2-methyl-3-oxobutyric acid ethyl ester (7.74g, 81%), mp 118-123°C.

A solution of the amino ester from above (7.7g, 26.6mmol) and 2,6-dichlorophenylisothiocyanate (5.43g, 26.6mmol) in THF (150mL) was stirred at room temperature for 5h. Mercuric oxide (6.34g, 29.3 mmol) was then added in one portion, and stirring continued overnight. The mixture was filtered through diatomaceous earth, washing well with THF. The filtrate was evaporated, and the residue triturated with ether to give 2-[4-cyano-2-(2,6-dichlorophenylamino)-3-methyl-3*H*-benzimiazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester as an off-white solid (7.7g, 63%).

To a stirred mixture of conc. H_2SO_4 (40mL), HOAc (40mL) and water (40mL) at 60°C was added 2-[4-cyano-2-(2,6-dichlorophenylamino)-3-methyl-3*H*-benzimiazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester (7.4g, 16mmol) in one portion. The solution was heated at 100°C for 2.5h, then stirred overnight at room temperature. The reaction mixture was poured onto ice, and neutralized with conc. NH_4OH, with ice cooling. The precipitate was filtered and washed well with water. The solid was slurried in MeOH, stirred well, filtered, washed with MeOH until washings were colorless, and dried. The

title compound was obtained as a grey solid (5.48g, 88%), mp >300°C; MS (NH_3 CI) 387, 389 (MH+).

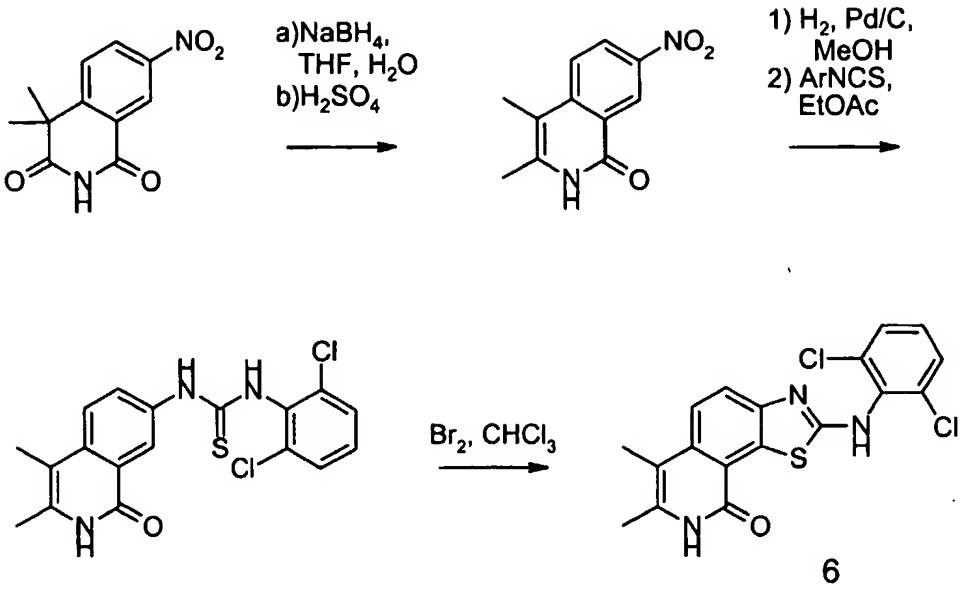
Example 5: Synthesis of 2-(2,6-Dichlorophenylamino)-6,6-dimethyl-6*H*-thiazolo[4,5-*h*]isoquinoline-7,9-dione (Method B).



5

To a suspension of 7-amino-4,4-dimethyl-2*H*,4*H*-isoquinoline-1,3-dione (204mg, 1mmol) in EtOAc (25mL) was added 2,6-dichlorophenylisothiocyanate (223mg, 1.1mmol) in three portions, and the mixture was stirred overnight. The solid was filtered and dried to yield the thiourea (380mg, 93%), mp 142-144°C; MS (CI) 408(MH^+). To a suspension of the thiourea (140mg, 0.34mmol) in $CHCl_3$ (20mL) was added Br_2 (60mg, 0.37mmol) in $CHCl_3$ (2mL) dropwise. The solution was heated to reflux for 1h. The solvent was evaporated and the residue triturated with saturated $NaHCO_3$ (50mL). The solid was filtered, washed with water, and dried, to yield the title compound (114mg, 82%), mp >300°C; MS (CI) 406(MH+).

Example 6: Synthesis of 2-(2,6-Dichlorophenylamino)-6,7-dimethyl-8*H*-thiazolo[4,5-*h*]isoquinoline-9-one (Method B).



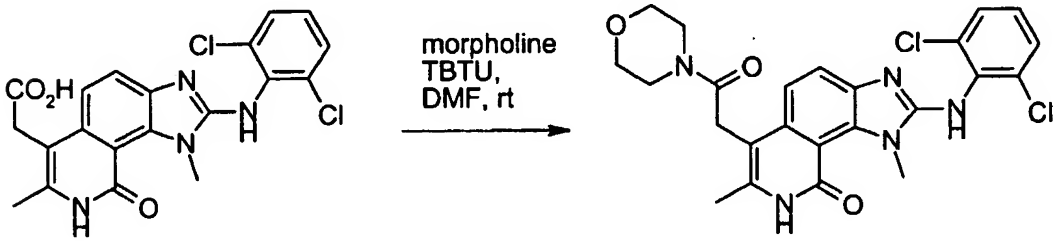
6

To a solution of 7-nitro-4,4-dimethyl-2*H*,4*H*-isoquinoline-1,3-dione from Example 1 (1.0g, 4.3mmol) in THF (50mL) was added $NaBH_4$ (330mg, 8.7mmol) followed by water (10 drops). The reaction mixture was stirred at room temperature for 2.5h, cooled in an ice bath and treated with 1N HCl until a pale yellow color was maintained. After 10 min. the reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine, dried and evaporated to the alcohol, which was immediately taken up in conc. H_2SO_4 (8mL). This mixture was stirred until completely dissolved (10 min.), poured over ice, neutralized with 10% NH_4OH, allowed to stand several hours, filtered and dried to yield 3,4-dimethyl-7-nitro-isoquinoline-1-one (780mg, 83%). MS (CI) 219(MH^+).

A solution of 3,4-dimethyl-7-nitro-isoquinoline-1-one (750mg, 3.4mmol) in MeOH (250mL) was hydrogenated over Pd/C (25mg) at 60psi for 24h. The reaction mixture was filtered through diatomaceous earth, washing well with MeOH. Evaporation of the filtrate provided the amine (554mg, 85%) which was immediately dissolved in EtOAc (60mL) and treated with 2,6-dichlorophenylisothiocyanate (663mg, 3.3mmol). The mixture was stirred at ambient temperature for 48h, refluxed for 4h and stirred at ambient temperature an additional 72h. The thiourea was filtered and washed with EtOAc (850mg, 74%). mp 220°C (dec). A portion of the thiourea (490mg, 1.25mmol) was

suspended in $CHCl_3$ (50mL) and treated with a solution of Br_2 (200mg, 1.25mmol) in $CHCl_3$ (5mL), and the resulting mixture was refluxed for 1h. The solvent was evaporated, the residue was suspended in a saturated solution of $NaHSO_3$, filtered, then treated analogously with a saturated solution of $NaHCO_3$. Purification by silica column chromatography (0 to 5% MeOH in CH_2Cl_2 eluant) yielded the title compound (281mg, 58%), mp >300°C, MS (CI) 390 (MH^+).

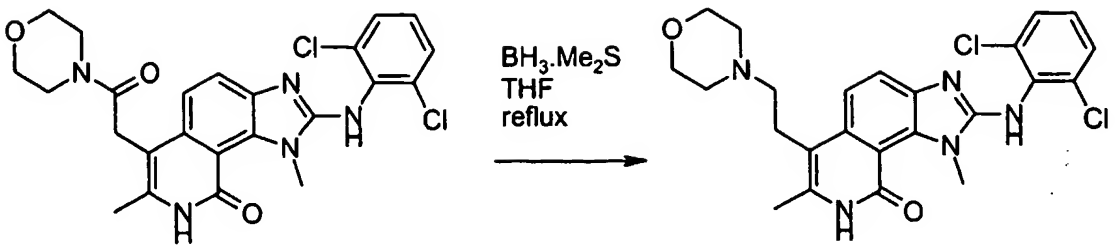
Example 7: Synthesis of 2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-morpholin-4-yl-2-oxoethyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.



7

To a solution of 2-(2,6-dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-6-yl acetic acid (prepared using Methods C and A) (1.0g, 2.3mmol) in DMF (7mL) was added *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.82g, 2.6mmol) and morpholine (0.24mL, 2.8mmol), and the mixture stirred 18h at room temperature. Ice water was added, the precipitate collected, washed with water and dried to give the title compound, 0.97g, 84%, mp >300°C; MS (ES) 500, 502 (MH+).

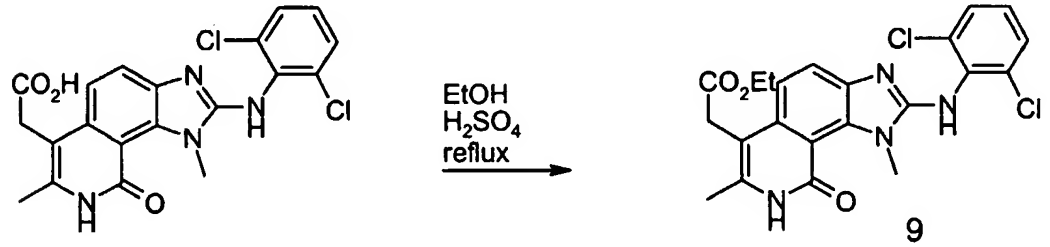
Example 8: Synthesis of 2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-morpholin-4-yl-ethyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.



7 8

A stirred suspension of the product of Example 7 (85mg, 0.17mmol) in THF (9mL) was heated to reflux and borane-methylsulfide (0.09mL, 0.9mmol) added. Stirring was continued for 3.5h at reflux and overnight at room temperature. 6M HCl was added and the solution stirred for 2h. The solution was applied to a Varian SCX column, washed with MeOH/CH_2Cl_2 50:50, then the product eluted with MeOH/CH_2Cl_2/NH_4OH 50:50:1. The product was further purified on a silica column eluting with CH_2Cl_2/MeOH 98:2 to give the title compound 32mg, 39%, mp 285-290°C; MS (ES) 486, 488 (MH+).

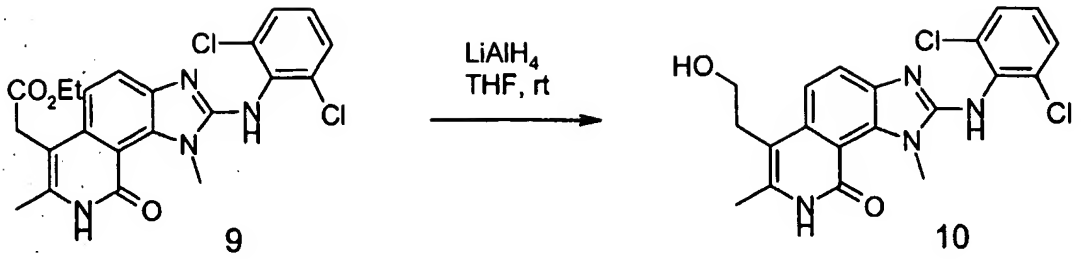
Example 9: Synthesis of 2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-6-yl acetic acid ethyl ester.



9

Prepared from 2-(2,6-dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-6-yl acetic acid by refluxing in ethanol and H_2SO_4. Mp 280-285°C (dec); MS(CI) 459, 461 (MH+).

Example 10: Synthesis 2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-hydroxyethyl)-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.

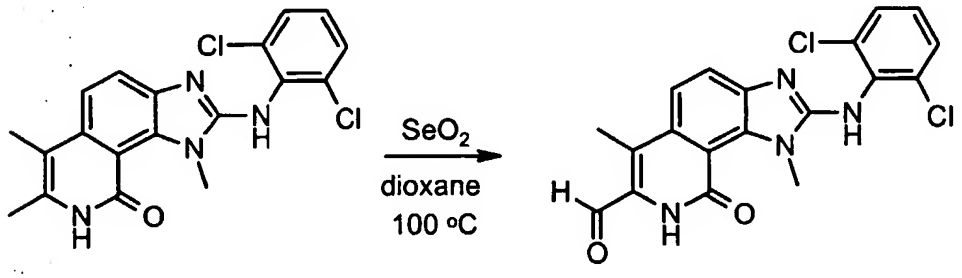


9 10

To a stirred solution of the product of Example 9 (25mg, 0.05mmol), in THF (2mL), under nitrogen, was added a solution of lithium aluminum hydride (1M in THF, 0.25mL, 0.25mmol). The mixture was stirred for 30min at room temperature. Ethyl acetate was added, followed by water, and then acidified with 1N HCl. The whole mixture was applied to a Varian SCX cartridge, and washed in turn with 1N HCl, water, acetone, MeOH, and MeOH/CH_2Cl_2 (1:1). The product was then eluted with MeOH/CH_2Cl_2 /NH_4OH (49:49:2). Evaporation of the eluent gave the title compound (15mg, 72%). Mp >300°C; MS(ES) 417, 419 (MH+).

Example 11: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-*h*]isoquinoline-7-carbaldehyde.

The method described below is useful for preparing intermediate compounds such as 11, which possess an aldehyde moiety at the 7-position.

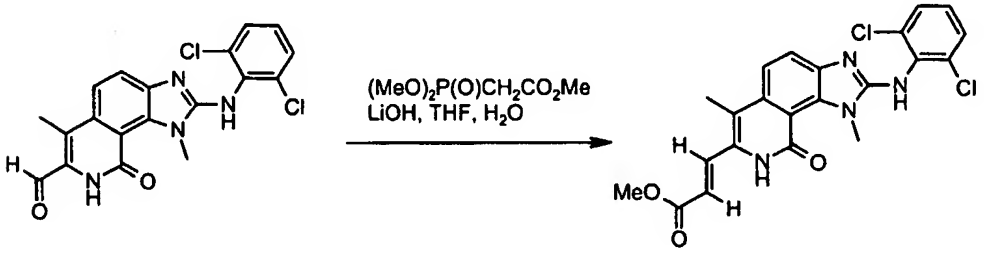


4 11

To a suspension of the product from Example 4 (521mg, 1.3mmol) in dioxane (30mL) was added selenium dioxide (430mg, 3.9mmol) and the mixture was heated at 100°C for

5h. The reaction was then cooled to room temperature, filtered through diatomaceous earth with 10% MeOH-CH_2Cl_2 and then concentrated in vacuo. The crude material was triturated with CH_2Cl_2 to provide the title compound (476mg, 92%), mp: >300°C; MS (CI) 401, 403 (MH+).

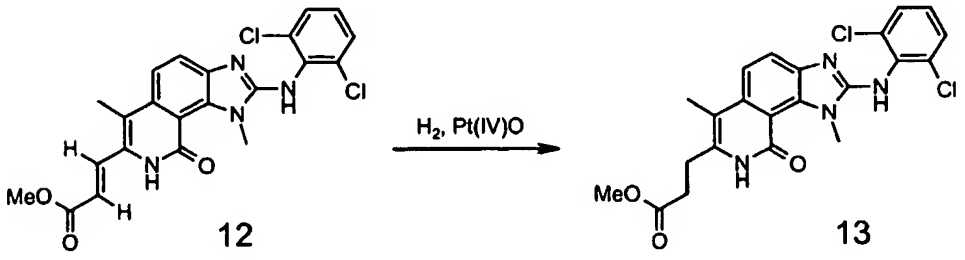
Example 12: Synthesis of 3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-*h*]isoquinolin-7-yl]-acrylic acid methyl ester.



11 12

To a suspension of the product of Example 11 (329mg, 0.82mmol) in THF (5mL) was added sequentially, trimethyl phosphonoacetate (164mg, 0.90mmol), lithium hydroxide monohydrate (76mg, 1.8mmol) and water (0.9mL). The blood red solution was stirred for 2h, quenched with water, and the resulting solid was collected and dried in vacuo. Column chromatography (5% MeOH-CH_2Cl_2) provided the title compound (300mg, 80%), mp >300°C; MS (ES) 457, 459 (MH+).

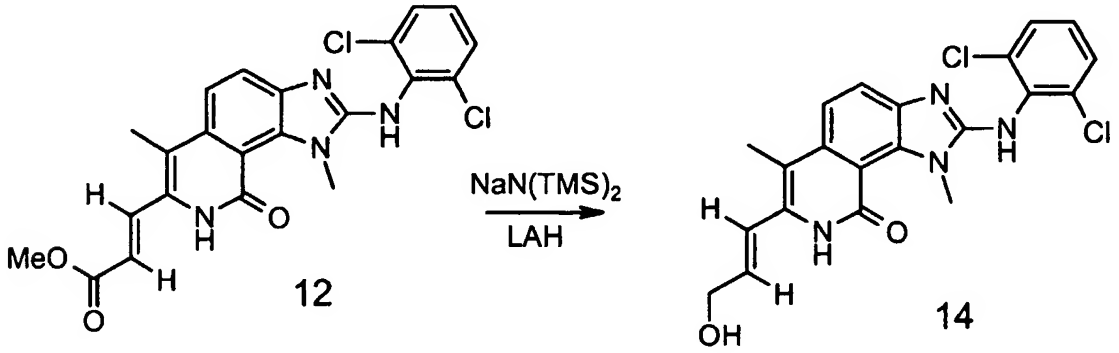
Example 13: Synthesis of 3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-*h*]isoquinolin-7-yl]-propionic acid methyl ester.



12 13

To a solution of the product of Example 12 (30mg, 0.06mmol) in EtOH (3mL) and AcOH (4mL) in a Parr reactor was added PtO_2 (2mg, 0.007mmol). The Parr reactor was charged with 50psi of H_2 and shaken for 12h. The crude reaction was filtered through diatomaceous earth with EtOH and concentrated in vacuo. Column chromatography (2% MeOH-CH_2Cl_2) provided the title compound (9mg, 30%), mp 268°C(dec); MS(ES) 459, 461(MH+).

Example 14: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-hydroxy-propen-1-yl)-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-9-one.



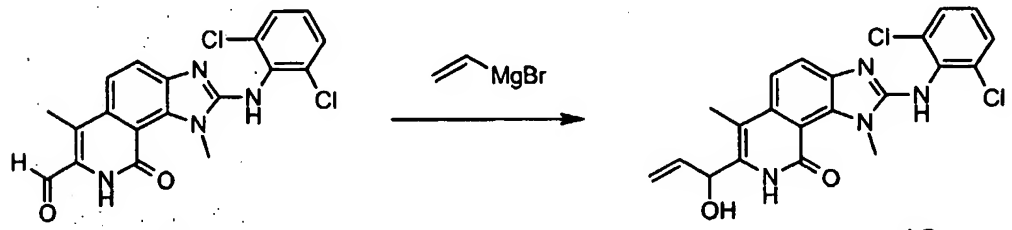
A suspension of the product of Example 12 (100mg, 0.22mmol) in THF (7mL) was cooled to –78°C. Sodium bis(trimethylsilyl)amide (1M in THF, 0.44mmol) was added dropwise. The bright red solution was warmed to 0°C for 15 minutes, then lithium aluminum hydride (1M in THF, 2.6mmol) was added and the orange solution was warmed to room temperature for 0.5h. The mixture was cooled to 0°C, quenched with saturated ammonium chloride and extracted with ethyl acetate. Column chromatography (3-6% MeOH-CH_2Cl_2) provided the title compound (32 mg, 34%), mp 298-300°C; MS(ES) 429, 431(MH+).

Example 15: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-vinyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.

11 15

To a suspension of the product of Example 11 (100mg, 0.25mmol) in THF (5mL) was added trimethylsilylmethyl magnesium chloride (2mL, 2mmol) at –78°C. The reaction was warmed to room temperature for 1h, then cooled to 0°C and quenched with water and extracted with ethyl acetate to provide the silyl alcohol (85 mg, 70%). The crude silyl alcohol was suspended in CH_2Cl_2 and cooled to 0°C. Borontrifluoride etherate (42μL, 0.32mmol) was added and the slurry was warmed to room temperature for 1 h. The reaction was quenched with water, and the CH_2Cl_2 was removed in vacuo. Collection of the resulting solid followed by CH_2Cl_2 trituration provided the title compound (17mg, 61%), mp > 300°C; MS(Es) 399, 401(MH+).

Example 16: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(1-hydroxyprop-2-en-1-yl)-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-9-one.

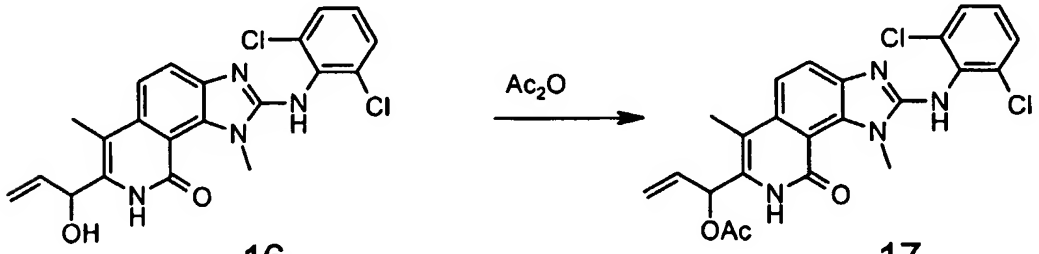


11 16

A suspension of 2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-*h*]isoquinoline-7-carbaldehyde (2) (100mg, 0.25mmol) in THF (3ml) was cooled to –78°C. Vinylmagnesium bromide (1M in THF, 2.0mmol) was added dropwise, and the brown suspension was warmed gradually to -10°C over 2h. The solution was quenched with saturated ammonium chloride and extracted with ethyl acetate, and

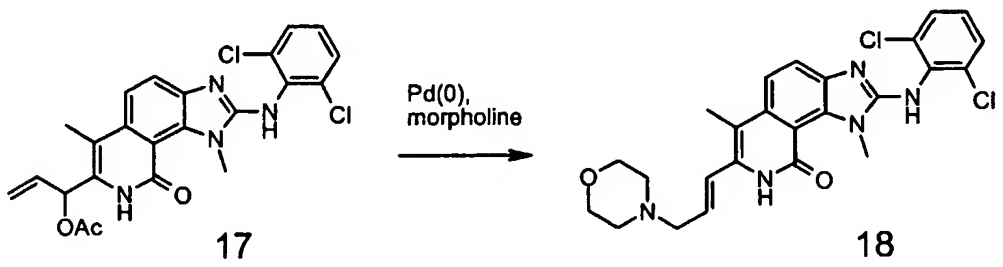
concentrated in vacuo to provide the title compound, which was used in the next step without purification, mp 235-236°C, MS (ES) 429 (MH+).

Example 17: Synthesis of 2-(2,6-Dichlorophenylamino)-7-(1-acetoxyprop-3-en-1-yl)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-9-one.



To a solution of the product of Example 16 (106mg, 0.25mmol) in THF (1ml) was added acetic anhydride (1ml). Triethylamine (35μL, 0.25mmol) was added, and the reaction was stirred for 14h, then concentrated in vacuo. Column chromatography (2% MeOH-CH_2Cl_2) provided the title compound (85mg, 79%), mp 169-171°C; MS (ES) 471 (MH+).

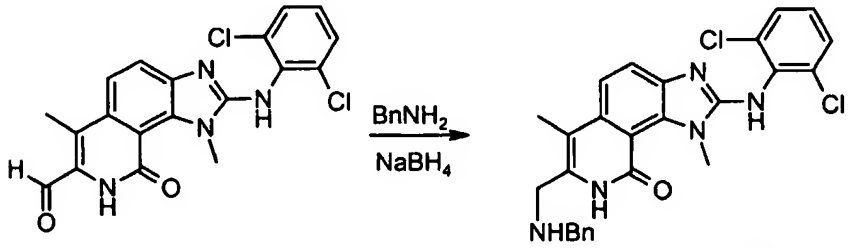
Example 18: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-morpholin-4-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one.



Tris(dibenzylideneacetone) dipalladium(0) (1.8mg, 0.002mmol) and triphenylphosphine (1.6mg, 0.006mmol) were stirred in THF (0.5ml) for 20min under inert atmosphere until the red solution turned yellow. To this solution was added sequentially, the product of Example 17 (20mg, 0.04mmol) in THF (0.5 ml), triethylamine (17μL, 0.12mmol) and morpholine (11μL, 0.12mmol). The solution was stirred 14h, then concentrated to an oil.

Column chromatography (10% MeOH-CH_2Cl_2) provided the title compound (10 mg, 50%), mp 175-177°C; MS (ES) 498 (MH+).

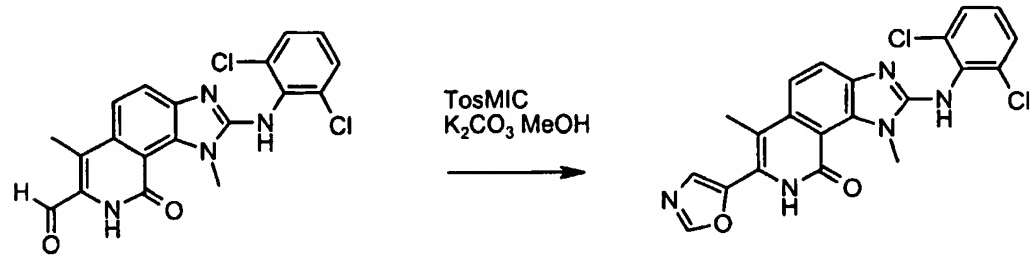
Example 19: Synthesis of 7-Benzylaminomethyl-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one.



11 19

To a suspension of the product of Example 11 (50mg, 0.12mmol) in THF (4mL) was added benzylamine (54mg, 0.50mmol). The reaction was stirred for 12h, then concentrated in vacuo. The crude imine was suspended in MeOH (2mL), sodium borohydride (21mg, 0.55mmol) was added, and the reaction was stirred for 3h. The reaction was quenched with water, and the resulting solid was collected and dried to provide the title compound (11mg, 39%), mp 231-234°C; MS (ES) 492(MH+).

Example 20: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-*h*]isoquinolin-9-one.

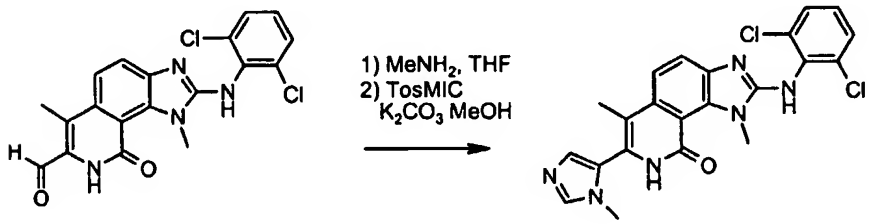


11 20

A suspension of the product of Example 11 (40mg, 0.10mmol), tosylmethyl isocyanide (21mg, 0.11mmol) and K_2CO_3 in methanol (2mL) was heated to 40°C for 90min. The

mixture was diluted with water (3mL) and the solid collected by filtration to obtain the title compound (26mg, 60 %), mp >300°C; MS (ES) 440, 442(MH+).

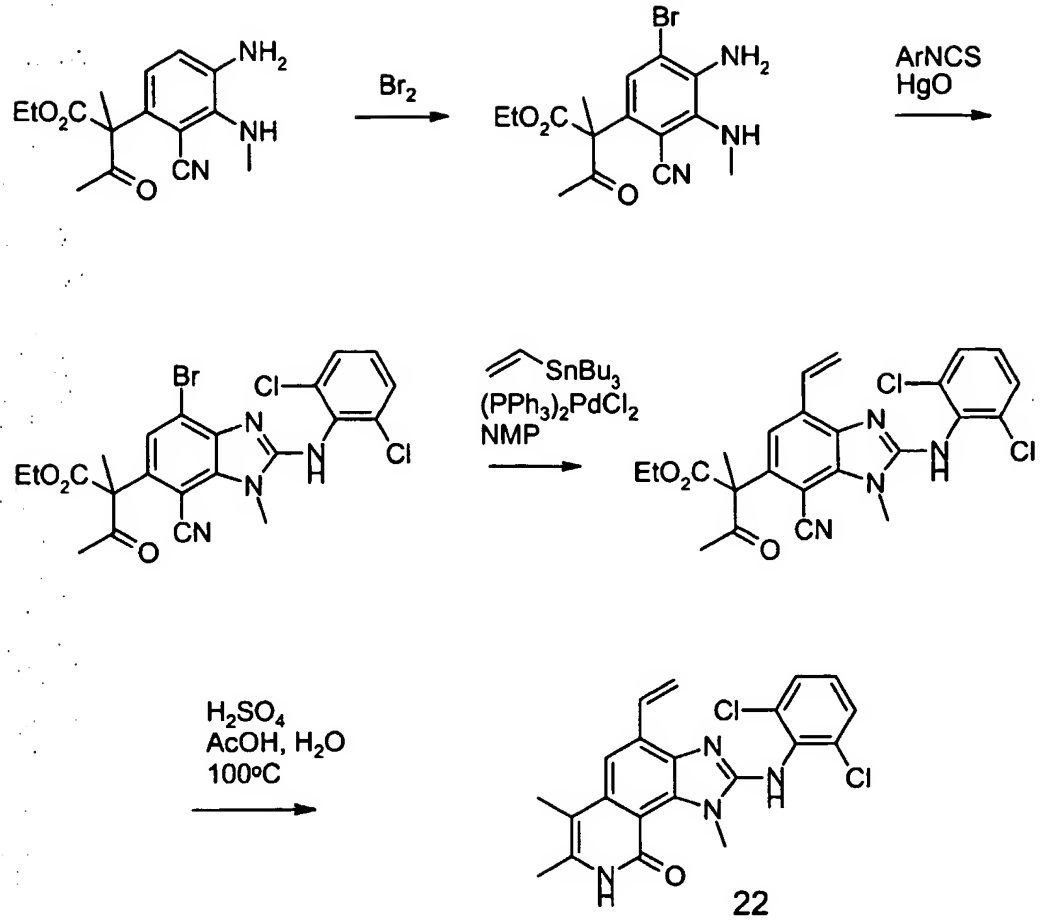
Example 21: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-methyl-3*H*-imidazol-4-yl)-1,8- dihydro-imidazo[4,5-*h*]isoquinolin-9-one.



11 21

A suspension of the product of Example 11 (50mg, 0.13mmol) and methylamine (2M in THF, 2mL, 4mmol) in dry THF (2mL) was stirred at room temperature for 12h. The THF was evaporated and the resulting imine was mixed with tosylmethyl isocyanide (27mg, 0.14mmol), K_2CO_3 (31mg, 0.23mmol) and dry DMSO (2mL). This suspension was stirred for five days at room temperature. Water (5mL) was added and the precipitate collected by filtration. Flash chromatography in CH_2Cl_2/MeOH (98:2) gave the title compound (8mg, 14%), mp >300°C; MS(ES) 453, 455 (MH+).

Example 22: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-4-vinyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.



22

To a solution of 2-(4-amino-2-cyano-3-methylaminophenyl)-2-methyl-3-oxobutyric acid ethyl ester from Example 4 (9.02g, 31.2mmol) in $CHCl_3$ (90mL) was added bromine (4.98g, 31.2mmol) dropwise at ambient temperature. After the addition of bromine, the reaction mixture was diluted with ethyl acetate (800mL). This solution was washed successively with sat. $NaHCO_3$ solution and brine and dried. The residue after evaporation was purified by flash chromatography in hexanes/EtOAc 2:1 to yield 2-(4-amino-5-bromo-2-cyano-3-methylaminophenyl)-2-methyl-3-oxobutyric acid ethyl ester as an oil (6.06g, 53%).

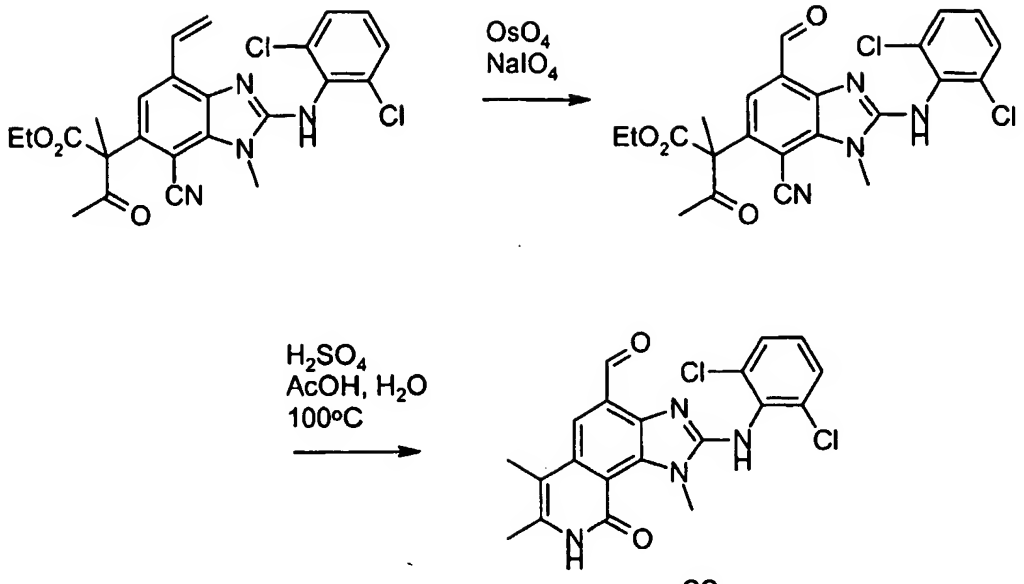
To a solution of the above ester (3.32g, 9.02mmol) in 1,4-dioxane (45mL) was added 2,6-dichlorophenylisothiocyanate (2.02g, 9.92mmol) and mercuric oxide (2.54g, 11.7mmol) under nitrogen atmosphere. The resulting mixture was stirred and heated at 95°C overnight. The reaction mixture was cooled to room temperature and filtered though a

short pad of diatomaceous earth and SiO_2. The filtrate was concentrated and the residue was purified by flash chromatography in hexanes/EtOAc 2:1 to yield 2-[8-bromo-4-cyano-2-(2,6-dichlorophenylamino)-3-methyl-3*H*-benzimiazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester as a brown solid (3.44g, 71%).

A mixture of the above bromo ester (600mg, 1.11mmol), $(PPh_3)_2PdCl_2$ (78mg, 0.11mmmol) and tributyl(vinyl)tin (0.49mL, 1.67mmol) in NMP (4mL) was degassed and heated at 100°C for 3 days under argon. The mixture was concentrated and the residue was purified by flash chromatography in hexanes/EtOAc 3:1 to yield 2-[4-cyano-2-(2,6-dichlorophenylamino)-3-methyl-8-vinyl-3*H*-benzimiazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester as an oil (530mg, 98%).

A solution of the above keto ester (66mg, 0.14mmol) in a mixture of H_2SO_4 (0.6mL), acetic acid (0.6mL) and water (0.6mL) was heated at 100°C for 2h. The resulting mixture was cooled to room temperature and diluted with water (10mL). The solution was adjusted to pH 8 with 10% NaOH solution. The precipitated brown solid was filtered and purified by flash chromatography in CH_2Cl_2/MeOH 30:1 to yield the title compound (15mg, 27%), mp decomp. above 250°C; MS (CI) 413(MH+).

Example 23: Synthesis of 2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-9-oxo-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-4-carbaldehyde.

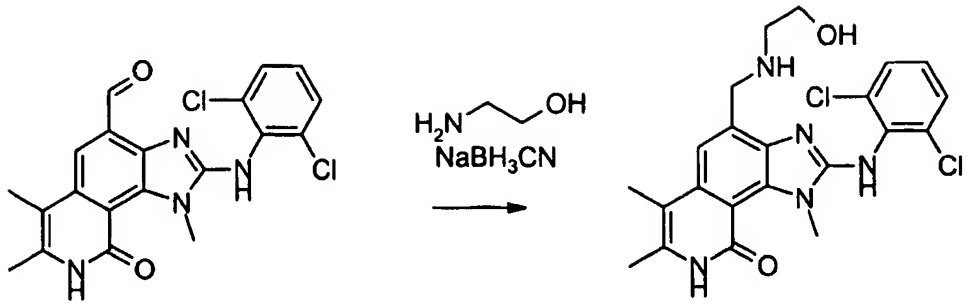


23

A solution of 2-[4-cyano-2-(2,6-dichlorophenylamino)-3-methyl-8-vinyl-3*H*-benzimiazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester (see Example 22) (538mg, 1.11mmol) in THF (30mL) was treated with 2.5% OsO_4 solution in tBuOH (3.0mL), $NaIO_4$ (712mg, 3.33mmol) and water (3mL). After stirring for 1.5h at room temperature, the mixture was diluted with EtOAc. The organic solution was washed with brine, dried and concentrated. The residue was purified by flash chromatography in hexanes/EtOAc 4:1 to yield 2-[4-cyano-2-(2,6-dichlorophenylamino)-8-formyl-3-methyl-3*H*-benzimiazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester as an oil 345mg, 64%).

A solution of the above aldehyde (35mg, 0.07mmol) in a mixture of H_2SO_4 (0.6mL), acetic acid (0.6mL) and water (0.6mL) was heated at 100°C for 1.5h and cooled to room temperature. The resulting mixture was diluted water (10mL) and the pH adjusted to 7 with ammonium hydroxide solution. The precipitated orange powder was filtered to give the title compound as an orange solid (18mg, 60%).

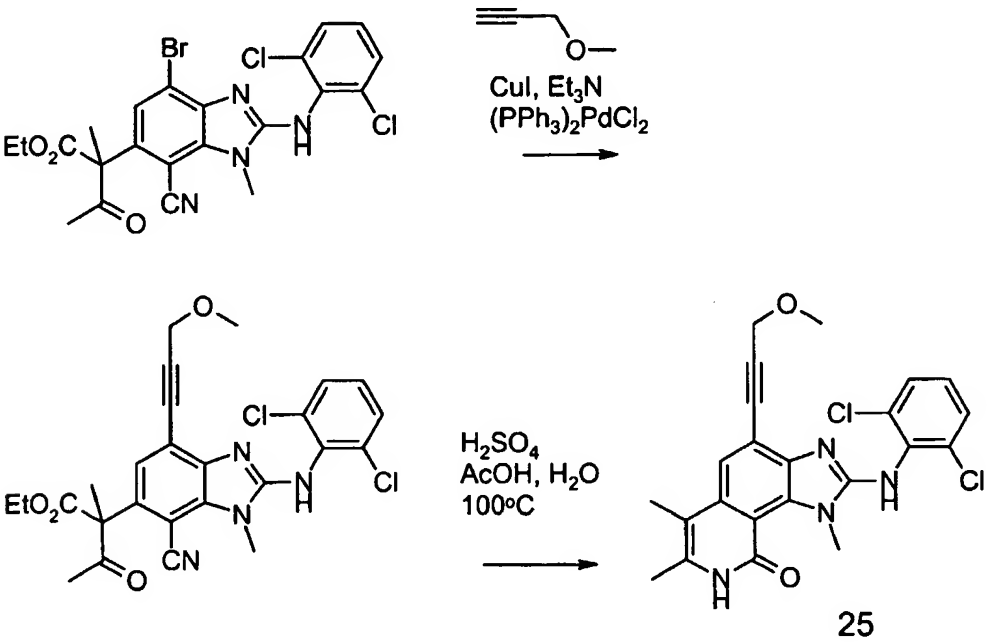
Example 24: Synthesis of 2-(2,6-Dichlorophenylamino)-4-(2-hydroxyethylaminomethyl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.



23 24

A suspension of the product of Example 23 (30mg, 0.07mmol) in MeOH (5mL) was treated with ethanolamine (44μL, 0.72mmol) and $NaBH_3CN$ (14 mg, 0.22mmol), and stirred at room temperature for 16h. The resulting mixture was concentrated and the residue was diluted with water. The precipitated solid was filtered to give the title compound (12mg, 36%). mp decomp. above 250°C; MS (CI) 460 (MH+).

Example 25: Synthesis of 2-(2,6-Dichlorophenylamino)-4-(3-methoxypropyn-1-yl)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-*h*]isoquinoline-9-one.



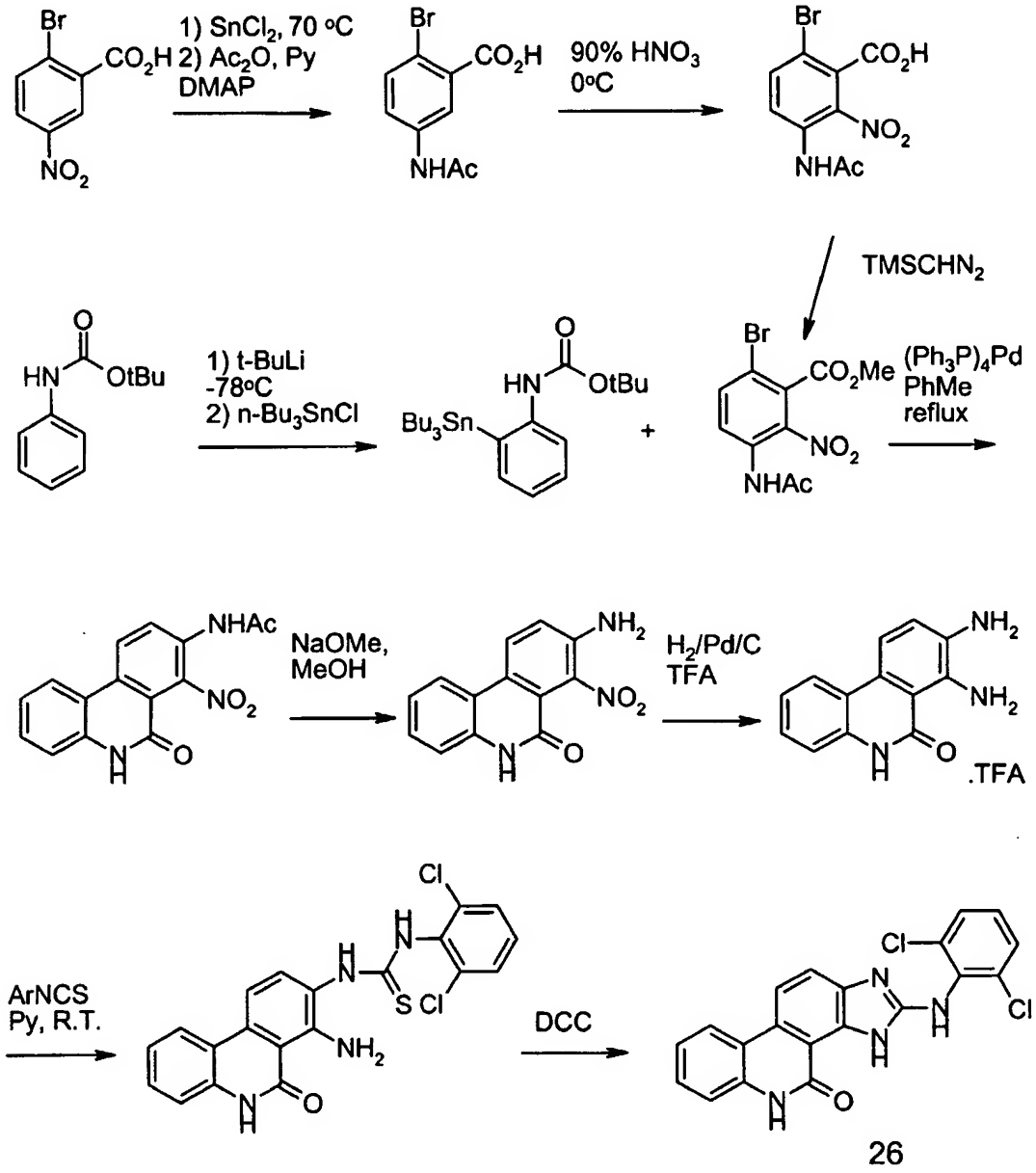
25

A mixture of 2-[8-bromo-4-cyano-2-(2,6-dichlorophenylamino)-3-methyl-3*H*-benzimidazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester (see Example 22) (50mg,

0.09mmol), methyl propargyl ether (16μL, 0.19mmol), $(PPh_3)_2PdCl_2$ (6.5mg, 0.009mmol) and CuI (3.5mg, 0.02mmol) in Et_3N (1mL) and THF(1mL) was stirred at room temperature for 5 days under argon. The resulting mixture was concentrated and the residue was purified by flash chromatography in hexanes/EtOAc 3:1 to give 2-[4-cyano-2-(2,6-dichlorophenylamino)-8-(4-methoxypropyn-1-yl)-3-methyl-3*H*-benzimidazol-5-yl]-2-methyl-3-oxobutyric acid ethyl ester as an oil (30mg, 61%).

A solution of the above ketoester (29mg, 0.006mmol) in a mixture of H_2SO_4 (0.4mL), acetic acid (0.4mL) and water (0.4mL) was heated at 100°C for 2h. The resulting mixture was cooled to room temperature and diluted with water (10mL). The pH of this solution was adjusted to 8 with 10% NaOH solution. The precipitated solid was filtered to give the title compound (17mg, 68%), mp decomp. above 250°C; MS(CI) 455 (MH+).

Example 26: Synthesis of 2-(2,6-Dichlorophenylamino)-3,5-dihydro-imidazo[4,5-*i*]phenanthridin-4-one.



To a solution of N-(*t*-butoxycarbonyl)aniline (2.0g, 10.35mmol) in dry THF (50mL) at –78°C, a solution of *t*-BuLi (2.7M in pentane, 26mL, 25.88mmol) was added dropwise over 30min. The resulting yellow solution was warmed to –20°C and stirred at this temperature for 2.5h. *n*-Bu_3SnCl (4.2mL, 15.52mmol) in dry THF (10mL) was added over 20min, and the solution stirred at –20°C for 2h, then at room temperature for 12h. The reaction mixture was poured into $NaHCO_3$ solution and extracted with ether. The

extract was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated and the resulting oil purified by flash chromatography in hexanes/ether (20:1) to give 2-tributylstannylphenylcarbamic acid *t*-butyl ester (2.42g, 54%).

Tin(II) chloride (46.67g, 206.84mmol) was added portionwise to a solution of 2-bromo-5-nitro benzoic acid (12.71g, 49.9mmol) in dry ethanol (200mL). The mixture was heated at 70°C for 45min, then ethanol was evaporated. The residue was cooled to 0°C, and acetic anhydride (43mL) and pyridine (26mL) were added. The solution was stirred at room temperature for 14h and evaporated. The residue was partitioned between aq. 2M HCl and ethyl acetate (400mL). The organic phase was washed with brine and dried over $MgSO_4$. The residue from evaporation was crystallized from water to give 5-acetylamino-2-bromobenzoic acid (12.4 g, 96 %).

5-Acetylamino-2-bromobenzoic acid (6.81 g, 26.39 mmol) was added portionwise to fuming nitric acid (90%, 11mL) at 0°C (as described by H. Goldstin, G. Preitner. *Helv. Chim. Acta* **1944**, *27*, 888). The ice bath was removed and the solution stirred at room temperature for 1.5h, then poured into ice water. 3-Acetylamino-6-bromo-2-nitro-benzoic acid was collected by filtration (5.07g, 63 %).

To a solution of 3-acetylamino-6-bromo-2-nitro-benzoic acid (3.86g, 14.96mmol) in dry THF (42mL) and dry methanol (18mL) was added a solution of (trimethylsilyl)diazomethane in hexane (2M, 24mL, 48mmol). The solution was stirred at room temperature for 3h and evaporated. The residue was purified by flash chromatography in hexanes/ethyl acetate (6:1) to give 3-acetylamino-6-bromo-2-nitrobenzoic acid methyl ester (2.45g, 52%).

A solution of 3-acetylamino-6-bromo-2-nitrobenzoic acid methyl ester (1.3g, 4. 11mmol) and $Pd(PPh_3)_4$ (0.31 g, 0.27 mmol) in dry toluene (15 mL) was stirred at room temperature for 10 min. To this orange solution was added a solution of 2-tributylstannylphenylcarbamic acid *t*-butyl ester (2.10 g, 4.94 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 14 h, during which time a precipitate

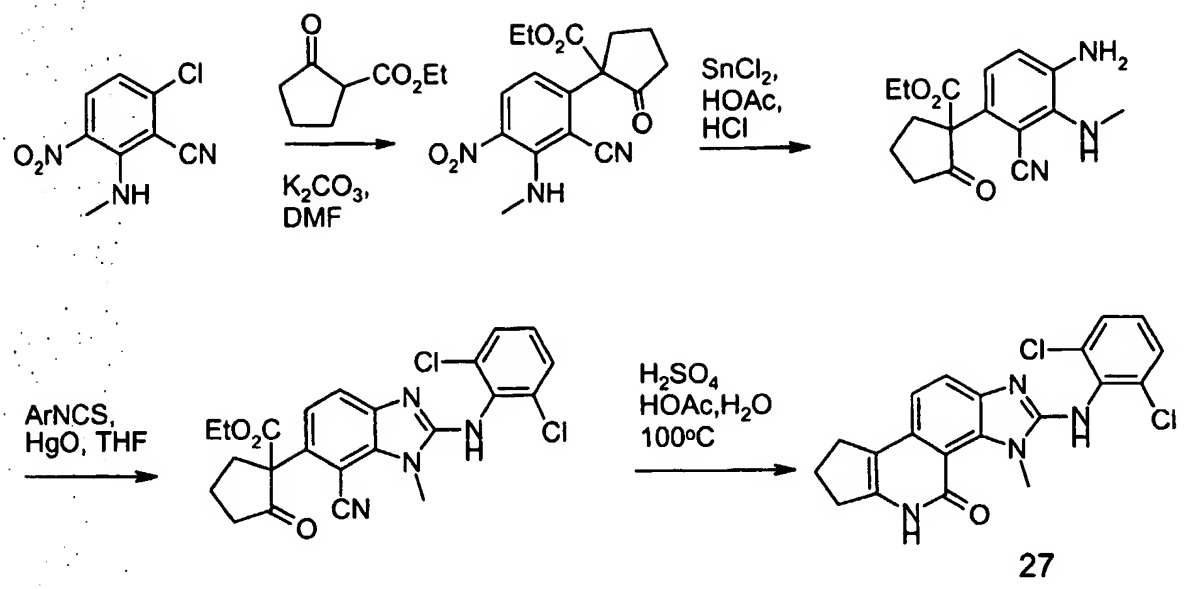
formed. 8-Acetamido-7-nitro-6-oxo-5,6-dihydro-phenanthridin-6-one was collected by filtration as an off-white solid (1.07g, 88%).

A suspension of 8-acetamido-7-nitro-6-oxo-5,6-dihydro-phenanthridin-6-one (770mg, 2.66mmol) and NaOMe (25% w/w solution in MeOH, 3.5mL, 6.64mmol) in dry methanol (15mL) was heated to reflux for 3h. The methanol was evaporated and the residue triturated with water and filtered to yield 8-amino-7-nitro-*5H*-phenanthridin-6-one (500mg, 74%).

A mixture of 8-amino-7-nitro-*5H*-phenanthridin-6-one (412mg, 1.62mmol), Pd/C (10 wt %, 234 mg) in TFA was hydrogenated at 50 psi for 50min. The catalyst was filtered through a plug of diatomaceous earth and rinsed with ethanol. The solvent was evaporated to obtain 7,8-diamino-*5H*-phenanthridin-6-one trifluoroacetate salt (520 mg, 71 %).

To a solution of 7,8-diamino-*5H*-phenanthridin-6-one trifluoroacetate salt (200mg, 0.44mmol) in pyridine (3mL) was added 2,6-dichlorophenylisothiocyanate (93mg, 0.46mmol). The suspension was stirred at room temperature for 14h. The pyridine was evaporated using a toluene azeotrope. The residue was triturated with ethanol to obtain the thiourea (150mg, 79%). A mixture of thiourea (146mg, 0.34mmol) and dicyclohexylcarbodiimide (83mg, 40.80mmol) in dry THF (2mL) and dry DMF (0.9mL) was heated to 80°C for 8h. The solvent was removed under high vacuum and the residue triturated with hot ethanol to give the title compound (82mg, 61%), mp >300°C; MS(CI) 395, 397(MH+).

Example 27: Synthesis of 2-(2,6-Dichlorophenylamino)-3-methyl-5,6,7,8-tetrahydro-3*H*-1,3,5-triaza-dicyclopenta[*a,f*]naphthalen-4-one.



27

A mixture of 6-chloro-2-methylamino-3-nitrobenzonitrile (200mg, 0.95mmol) (Example 4), ethyl 2-oxocyclopentanecarboxylate (177mg, 1.13mmol) and K_2CO_3 (287mg, 2.07mmol) in DMF (5mL) was stirred at room temperature for 60h. The mixture was diluted with sat. NH_4Cl solution and extracted with ether. The ethereal layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography on silica (hexanes: EtOAc = 3:1) to give ethyl 1-(2-cyano-3-methylamino-4-nitrophenyl)-2-oxo-cyclopentanecarboxylate (127mg, 40%) as a yellow solid.

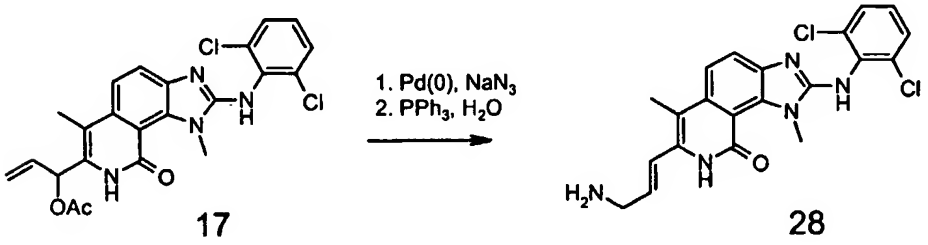
To a solution of the above compound (100mg, 0.30mmol) in acetic acid (1mL) was added a solution of tin (II) chloride dihydrate (681mg, 3.0mmol) in c. HCl (0.5mL) at room temperature. The resulting mixture was stirred at room temperature for 2h and quenched with sat. $NaHCO_3$ solution. The pH of the mixture was adjusted to 8 with $NaHCO_3$. The product was extracted into EtOAc and the organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated to give ethyl 1-(4-amino-2-cyano-3-methylaminophenyl)-2-oxo-cyclopentanecarboxylate (76mg, 84%) as a yellow oil.

A mixture of the above diamine (140mg, 0.46mmol), 2,6-dichlorophenyl isothiocyanate (104mg, 0.51mmol) and HgO (110mg, 0.51mmol) in THF (5mL) was refluxed for 8h. The cooled mixture was filtered through diatomaceous earth and concentrated. The

residue was diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica in hexanes/EtOAc, (1:1) to give ethyl 1-[4-cyano-2-(2,6-dichlorophenylamino)-3-methyl-3*H*-benzimidazol-5-yl]-2-oxo-cyclopentanecarboxylate (200mg, 92%) as a light yellow solid.

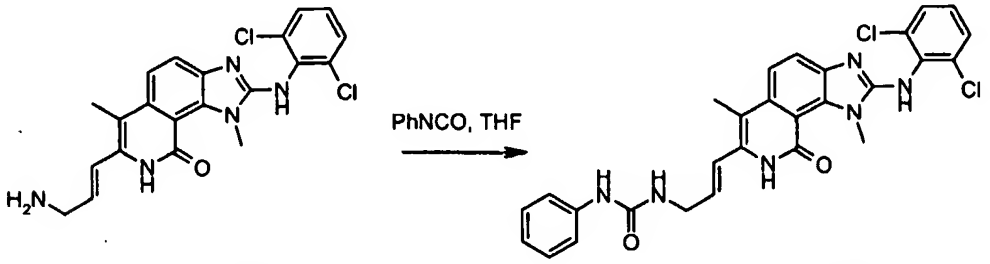
A solution of the above benzimidazole (195mg, 0.41mmol) in a 1:1:1 mixture of water, acetic acid and H_2SO_4 (1.5mL) was heated at 100 °C for 3h. The reaction mixture was cooled and diluted with water. The precipitate was collected and washed with water. The collected yellow solid was purified by chromatography on SiO_2 in CH_2Cl_2 /MeOH (20:1) to give the title compound (70mg, 43%) as a light yellow solid. Mp >300°C (dec.), MS (CI) m/z 399 (M^++H).

Example 28: Synthesis of 7-(3-Aminopropen-1-yl)-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one.



A suspension of tris(dibenzylideneacetone) dipalladium(0) (185mg, 0.25mmol) and triphenylphosphine (320mg, 1.2mmol) in THF (40mL) was stirred for 20 min under N_2. A solution of the product from Example 17 (1.88g, 4.0mmol) in THF (5 mL) was added and the mixture stirred for 20 min. Sodium azide (280mg, 4.4mmol) and water (4.0mL) were added and the reaction was heated at 60°C for 3h. The solution was cooled to rt and triphenylphosphine (1.0g, 3.8mmol) was added. After stirring for 45 min., ammonium hydroxide (4 mL) was added and stirring continued overnight. The resulting solution was dried over $MgSO_4$, then concentrated to an oil. Column chromatography on silica eluting with CH_2Cl_2/MeOH (90:10 increasing to 50:50) provided the title compound (1.2 g, 70%), mp >300°C; MS (ES) 428 (MH+).

Example 29: Synthesis of 1-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-3-phenyl urea.



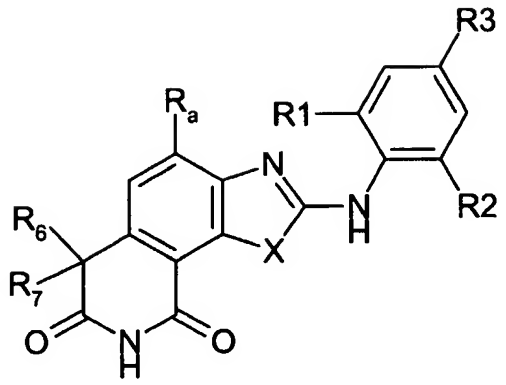
28 29

A solution of the product of Example 28 (50mg, 0.12mmol) and phenyl isocyanate (17mg, 0.13mmol) in DMF (2mL) was heated at 60°C for 10h. The resulting precipitate was filtered, triturated with MeOH/CH_2Cl_2 (90:10), and dried to provide the title compound (57 mg, 89%) mp >290°C; MS (ES) 547 (MH+).

Other Examples

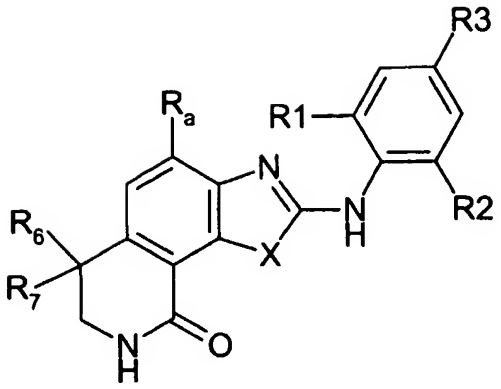
Using methods analogous to those described above, the following compounds of this invention (Tables 1-3) were prepared:

Table 1: Compounds of Formula I with R_4, R_5 = C



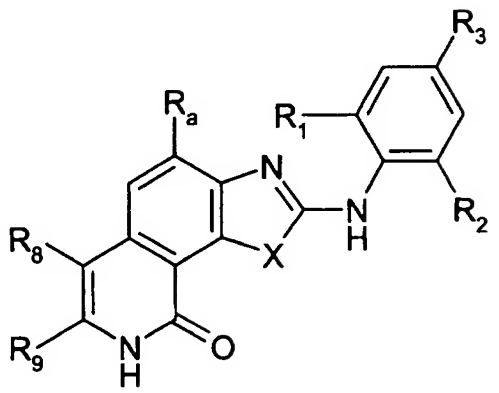
Example	X	R_1	R_2	R_3	R_a	R_6	R_7	m.p. °C
30	NH	Me	Cl	H	H	Me	Me	>300
31	NH	Cl	Cl	Cl	H	Me	Me	>275
32	NH	Me	Me	H	H	Me	Me	>300

Table 2: Compounds of Formula I with R_4, R_5 = A



Example	X	R_1	R_2	R_3	R_a	R_6	R_7	m.p. °C
33	NH	Cl	Cl	H	H	H	H	172-178

Table 3: Compounds of Formula I with R_4, R_5 = B



Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
34	S	Cl	Cl	H	H	Me	Me	>300
35	NH	H	Cl	H	H	Me	Me	>300
36	NH	Cl	Cl	Cl	H	Me	Me	>250
37	NH	Br	Br	Br	H	Me	Me	>250
38	NH	Cl	Me	H	H	Me	Me	>250
39	NH	Cl	Cl	H	H	H	*n*-Pr	>250
40	NH	Cl	Cl	H	H	CO_2Et	Me	265
41	NH	Cl	Cl	H	H	Me	CHO	>300
42	NH	Cl	Cl	H	H	CH_2CO_2Et	Me	292-296

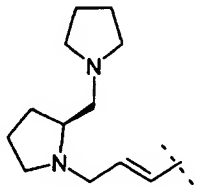
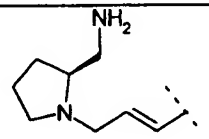
Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
43	NH	Cl	Cl	H	H	H	Me	>300
44	NH	Cl	Cl	H	H	Me	CH_2OH	>300
45	NH	Cl	Cl	OMe	H	Me	Me	>300
46	NH	Cl	Cl	H	H	CH_2CO_2H	Me	>250
47	NMe	Cl	Cl	H	H	Me	$CH_2NH(CH_2)_2NEt_2$	194-196
48	NMe	Cl	Cl	H	H	Me	CH_2OH	>280
49	NMe	Cl	Cl	H	H	Me	CH_2NHMe	263-265
50	NMe	Cl	Cl	H	H	Me	$CH_2NH(CH_2)_2OMe$	215-218
51	NMe	Cl	Cl	H	H	Me	CH_2(4-morpholinyl)	292-295
52	NMe	Cl	Cl	H	H	CH_2CO_2Et	Me	280-285
53	NMe	Cl	Cl	H	H	$CH_2C(O)NHEt$	Me	>300
54	NMe	Cl	Cl	H	H	$CH_2C(O)$ NMe_2	Me	>300
55	NMe	Cl	Cl	H	H	$CH_2C(O)NH$-CH_2Ph	Me	>300
56	NMe	Cl	Cl	H	H	$CH_2C(O)NH$-$(CH_2)_2$ NEt_2	Me	298-302
57	NMe	Cl	Cl	H	H	$CH_2C(O)NH$-$(CH_2)_2Ph$	Me	>300
58	NMe	Cl	Cl	H	H	$CH_2C(O)$(4Me-piperazin-1-yl)	Me	>300

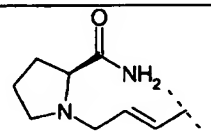
Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
59	NMe	Cl	Cl	H	H	$CH_2C(O)$ $NH(CH_2)_3$ NEt_2	Me	267.5-270
60	NMe	Cl	Cl	H	H	CH_2CH_2OH	Me	>300
61	NMe	Cl	Cl	H	H	$CH_2C(O)$(4-morpholinyl)	Me	>300
62	NMe	Cl	Cl	H	H	$CH_2C(O)NH(CH_2)_2$ (4-morpholinyl)	Me	277-283
63	NMe	Cl	Cl	H	H	H	$CH=CHCO_2Me$	>300
64	NMe	Cl	Cl	H	H	$CH_2C(O)NH$-$(CH_2)_2NEt_2$	Me	>262
65	NMe	Cl	Cl	H	H	$(CH_2)_2CO_2H$	Me	295-305
66	NMe	Cl	Cl	H	H	$(CH_2)_2CO_2Et$	Me	268-273
67	NH	Cl	Cl	H	H	$CH_2C(O)$ NMe_2	Me	>300
68	NMe	Br	Br	H	H	Me	Me	238-240
69	NMe	Cl	Cl	H	H	$(CH_2)_2OC(O)Me$	Me	>275
70	NMe	Cl	Cl	H	H	$CH_2C(O)NHCH_2$ (pyridin-2-yl)	Me	>300
71	NMe	Cl	Cl	H	H	$(CH_2)_2$(4-	Me	285-290

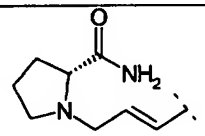
Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
						morpholinyl)		
72	NMe	Cl	Cl	H	H	$(CH_2)_2NHEt$	Me	253-262
73	NMe	Cl	Cl	H	H	$CH_2C(O)NH_2$	Me	>300
74	NMe	Cl	Cl	H	H	H	CH=CHC(O)N(OMe)Me	>300
75	NMe	Cl	CF_3	H	H	Me	Me	226-228
76	NMe	Cl	NO_2	H	H	Me	Me	278-280
77	NMe	Cl	Cl	H	C(O)Me	Me	Me	>300
78	NMe	Cl	Cl	H	H	H	$CH=CHC(O)NHCH_2Ph$	>300
79	NMe	Cl	Cl	H	C(OH)Me	Me	Me	308-311
80	NMe	Cl	Cl	H	H	$CH_2CH(OMe)_2$	Me	247-248
81	NMe	Cl	Cl	H	H	H	CH=CHC(O)(4-morpholinyl)	>300
82	NMe	Cl	Cl	H	H	$(CH_2)_3$(4-morpholinyl)	Me	277-282
83	NMe	Cl	Cl	H	CH_2OH	Me	Me	>300
84	NMe	Me	Me	H	H	Me	Me	315-318
85	NMe	Me	Et	H	H	Me	Me	289-291
86	NMe	Cl	Br	F	H	Me	Me	317-319
87	NMe	Cl	Cl	H	CH_2NH-CH_2-(4-	Me	Me	247-250

Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
					OMe)Ph			
88	NMe	Cl	Cl	H	(3-Me)Ph	Me	Me	220-223
89	NMe	Cl	Cl	H	$CH_2C(O)$-CH_2OH	Me	Me	285
90	NMe	Cl	Cl	H	H	Me	CH=CHC(O)NH-[4-O$(CH_2)_2NEt_2$]Ph	>300
91	NMe	Cl	Cl	H	H	H	CH=CHC(O)NHMe	>300
92	NMe	Cl	NH_2	H	H	Me	Me	300-302
93	NMe	Cl	Cl	H	$(CH_2)_3OH$	Me	Me	208-210
94	NMe	Cl	Cl	H	H	H	$CH=CH_2$	259-261
95	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$-4-morpholinyl	175-177
96	NMe	Cl	Cl	H	H	Me	CH=CHCN	>300
97	NMe	Cl	Me	H	H	H	Me	>300
98	NMe	Cl	Cl	H	H	H	5-oxazolyl	>300
99	NMe	Cl	Cl	H	H	$(CH_2)_3OH$	Me	265-275
100	NMe	Cl	Cl	H	H	H	$CH=CHCH_2OH$	285
101	NMe	Cl	Me	H	H	H	$CH=CHCH_2OH$	264-266
102	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2NEt_2$	150-153
103	NMe	Cl	Cl	H	H	Me	CH=CHCN	280
104	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$-(1-pyrrolidinyl)	170-173

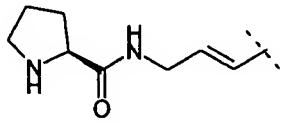
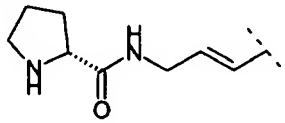
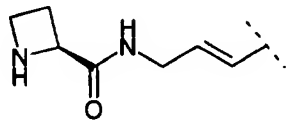
Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
105	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2N(Me)(CH_2Ph)$	134-136
106	NMe	Cl	Cl	OMe	H	Me	Me	>300
107	NMe	Cl	Cl	OMe	H	Me	5-oxazolyl	>300
108	NMe	Cl	Cl	OCF_3	H	Me	Me	>300
109	NMe	Cl	Cl	H	H	H	$CH=CHCH_2NEt_2$	130-131
110	NMe	Me	Me	H	H	H	Me	200
111	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$(4-Me-piperazin-4-yl)	251-253
112	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$(piperidin-1-yl)	159-161
113	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2N(Et)(CH_2CH_2OH)$	220-222
114	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2N(Me)(OH)$	185-186
115	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$(3-OH-pyrrolidin-1-yl)	160-163
116	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2N(n\text{-}Bu)_2$	122-125
117	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2N(Me)(MeOCH_2\text{-}CH_2)$	125-127
118	NMe	Me	Me	H	H	Me	$CH=CHCH_2NEt_2$	185-191
119	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2N(Me)(Et_2NCH_2\text{-}CH_2)$	119-121
120	NMe	Cl	Me	H	H	Me	$CH=CHCH_2NEt_2$	130-132
121	NMe	Cl	Me	H	H	Me	$CH=CHCH_2N(Me)(Et_2N(CH_2)_3)$	116-119
122	NMe	Cl	Me	H	H	Me	$CH=CHCH_2SCH_2CH_2NEt_2$	141-146
123	NMe	Cl	Me	H	H	Me	$CH=CHCH_2NMe_2$	245-247

Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
124	NMe	Cl	Me	H	H	Me	CH=CHCH$_2$N(Me)(cyclohexyl)	148-151
125	NMe	Cl	Me	H	H	Me	CH=CHCH$_2$N(Me)(i-Pr)	155-157
126	NMe	H	H	H	H	Me	Me	280dec
127	NMe	H	Cl	H	H	Me	Me	240 dec
128	NMe	H	H	Cl	H	Me	Me	>300
129	NMe	Cl	Cl	Cl	H	Me	Me	>300
130	NMe	Cl	H	H	H	Me	CH=CHCH$_2$NEt$_2$	144-146
131	NMe	Cl	Cl	Cl	H	Me	CH=CHCH$_2$NEt$_2$	197-199
132	NMe	H	H	H	H	Me	CH=CHCH$_2$NEt$_2$	172-175
133	NH	Cl	Cl	H	H	Me	5-oxazolyl	>300
134	NMe	Cl	Cl	H	H	Me	CN	>300
135	NMe	Cl	Cl	H	H	Me		135-137
136	NMe	Cl	Cl	H	H	Me		186-188

Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
137	NMe	Cl	Cl	H	H	Me		289-290
138	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$-(3-NH_2CO-piperidin-1-yl)	182-184
139	NMe	Cl	Cl	H	H	Me	$CH=NNMe_2$	>300
140	NMe	Cl	Cl	H	H	Me	CH=NNHMe	295-299
141	NMe	Cl	Cl	H	H	Me	$CH_2OC(O)Me$	>285
142	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$-(3-NH_2-pyrrolidin-1-yl)	200-202
143	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$-(3-MeC(O)NH-pyrrolidin-1-yl)	237-239
144	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$-(3-NMe_2-pyrrolidin-1-yl)	189-191
145	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$-(2-NH_2CO-piperidin-1-yl)	202-204
146	NMe	Cl	Cl	H	H	Me	CH=N(pyrrolidin-1-yl)	285-295dec
147	NMe	Cl	Cl	H	H	Me	$CH=NNHC(O)NH_2$	267-270dec
148	NMe	Cl	Cl	H	H	Me	$C(O)NH_2$	dec >228
149	NMe	Cl	Cl	H	H	Me	2,3-dihydrobenzimidazol -2-yl	dec. >240
150	NMe	Cl	Cl	H	H	Me	Benzimidazol-2-yl	248-252

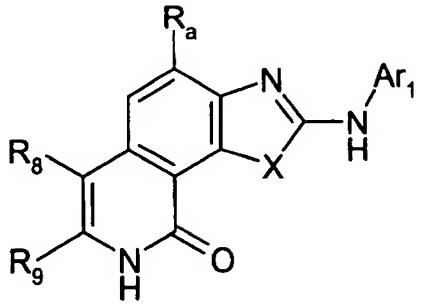
Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
151	NMe	Cl	Cl	H	H	Me	CH=NNHPh	>300
152	NMe	Cl	Cl	H	H	Me		264-265
153	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$(3-NH_2CH_2-piperidin-1-yl)	163-165
154	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2$(3-$NEt_2C(O)$-piperidin-1-yl)	169-171
155	NMe	Cl	Cl	H	H	Me	5-NH_2-benzimidazol-2-yl	dec. 290
156	NMe	Cl	Cl	H	H	Me	2,3-dihydro-1H-imidazo[4,5-c]pyridin-2-yl	>300
157	NMe	Cl	Cl	H	H	Me	imidazo[4,5-c]pyridin-2-yl	>300
158	NMe	Cl	Cl	H	H	Me	4-NH_2-benzimidazol-2-yl	dec > 290
159	NMe	Cl	Me	NH_2-C(O)	H	Me	Me	>300
160	NMe	Cl	Cl	H	H	Me	C≡CH	dec. >290
161	NMe	Cl	Cl	H	H	Me	$CH=CHCH_2NHC(O)NHMe$	>290
162	NMe	Cl	Cl	CF_3	H	Me	Me	>300
163	NMe	Cl	Cl	H	H	Me	CH(OH) cyclopentyl	285 (dec.)

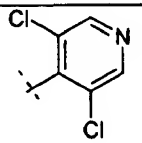
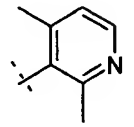
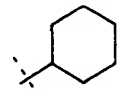
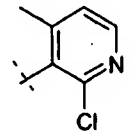
Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
164	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)cyclohexyl	>290
165	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)NH[2-MeOC(O)]Ph	>290
166	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NH C(O)NH[3-CN]Ph	>300
167	NMe	Cl	Cl	H	H	H	Ph	>250(dec)
168	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)Ph	> 290
169	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)NH[3-EtOC(O)]Ph	> 290
170	NMe	Cl	Cl	H	H	Me	Ph	> 300
171	NMe	Cl	Cl	H	H	EtOC(O)	Ph	283-284
172	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)NH[3-NO$_2$]Ph	> 290
173	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)NH[2-NO$_2$]Ph	> 290
174	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHS(O)$_2$Me	> 290
175	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)NH$_2$	> 290
176	NMe	Cl	Cl	H	H	Me	(cyclopenten-1-yl) CH$_2$	-
177	NMe	Cl	Cl	H	H	Me	(cyclopentylidene-1-yl)CH	-
178	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)NH(cyclohexyl)	> 290
179	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHSO$_2$Ph	> 290
180	NMe	Me	Me	OMe	H	Me	Me	
181	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHEt	218 - 221

Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
182	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NH C(=NH)NH$_2$	>290
183	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$(2,4-dioxo-quinazolin-3-yl)	>290
184	NMe	Cl	Cl	H	H	Me	(3-CO$_2$H)Ph	>300
185	NMe	Cl	Cl	H	H	Me	(3-Br)Ph	>300
186	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NHC(O)(piperidin-3-yl)	>290
187	NMe	Cl	Cl	H	H	Me		279 - 282
188	NMe	Cl	Cl	H	H	Me		
189	NMe	Cl	Cl	H	H	Me	[3-NH$_2$C(O)]Ph	>300
190	NMe	Cl	Cl	H	H	Me		> 290
191	NMe	Cl	Cl	H	H	Me	CH=CHCH$_2$NH C(O)(piperidin-2-yl)	269 - 273
192	NMe	Cl	Cl	H	H	Me	(3-CN)Ph	> 300
193	NMe	Cl	Cl	H	H	Me	(3-NH$_2$CH$_2$)Ph	241-246
194	NH	Me	Me	OMe	H	Me	Me	foam
195	NMe	Cl	Cl	H	H	Me	(3-NH$_2$C(=NH)NHCH$_2$)Ph	245-253

Ex	X	R_1	R_2	R_3	R_a	R_8	R_9	m.p. °C
196	NPr	Cl	Cl	H	H	Me	Me	280-281
197	NEt	Cl	Cl	H	H	Me	Me	>300

Table 4: Compounds of Formula I with R_4, R_5 = B



Ex.	X	Ar_1	R_a	R_8	R_9	m.p. °C
198	NH		H	Me	Me	>300
199	NH		H	Me	Me	>300
200	NMe		H	Me	Me	335(dec)
201	NMe		H	Me	Me	295(dec)

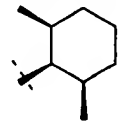
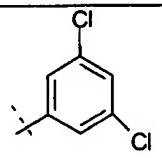
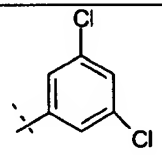
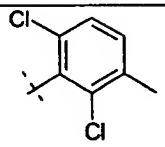
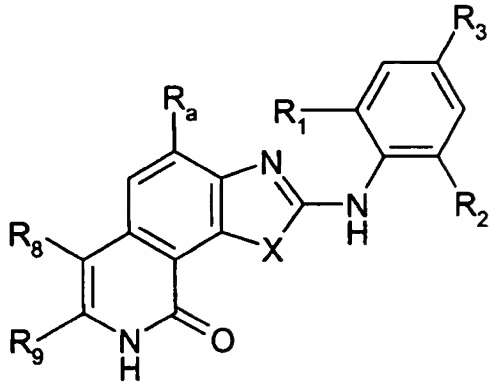
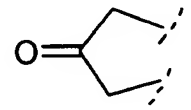
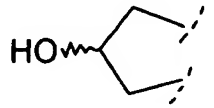
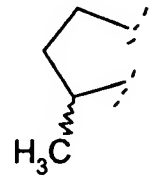
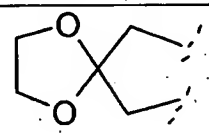
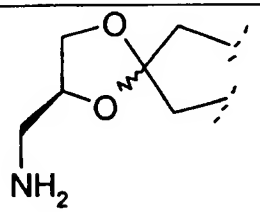
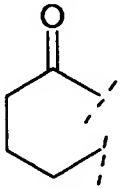
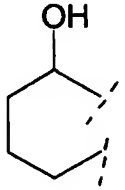
Ex.	X	Ar_1	R_a	R_8	R_9	m.p. °C
202	NMe		H	Me	Me	268-269
203	NMe		H	Me	Me	>300
204	NMe		H	Me	$CH=CHCH_2NEt_2$	250 (dec)
205	NMe		H	Me	Me	>300

Table 5: Compounds of Formula I wherein R_4, R_5 = B and R_8 and R_9 together form a ring



Ex	X	R_1	R_2	R_3	R_a	R_8 and R_9	m.p. °C
206	NMe	Cl	Cl	H	H		>300
207	NMe	Cl	Cl	H	H		>300
208	NMe	Cl	Cl	H	H		>300

Ex	X	R_1	R_2	R_3	R_a	R_8 and R_9	m.p. °C
209	NMe	Cl	Cl	H	H		>300
210	NMe	Cl	Cl	H	H		foam
211	NMe	Cl	Cl	H	H		>300
212	NMe	Cl	Cl	H	H		>300

Assessment of Biological Properties

Tyrosine Kinase Inhibition Assay

The inhibition of tyrosine kinases by the compounds of the invention was measured with the following assay.

Kinase Reaction Buffer 50mM Hepes, pH 7.5, 50mM KCl, 25mM $MgCl_2$, 5mM $MnCl_2$, 100 μM, Na_3VO_4, .01% CHAPS, 1mM DTT, and 50mg/mL BSA, Adenosine 5'-Triphosphate (ATP) solution at 100mM, pH 7.5 -γ33P-ATP, 2000 Ci/mmol at 10μCi/μl, -Poly(L-glutamic acid-L-tyrosine, 4:1) or $(E4Y)_n$ at 10mg/mL in water.

Assay: Test compounds, obtained routinely at 5mg/mL in 100% DMSO were diluted appropriately into complete Kinase assay buffer with 10% DMSO, 10μl of the 6Xcompound solution was distributed into each assay well, the final compound concentration for IC_{50} determinations ranged from 200 to 1μg/mL. [γ33P]-ATP label was prepared as a 10 Ci/mmol working solution in complete Kinase assay buffer. Protein kinase was initiated by adding 10 to 50ηg of diluted enzyme stock.

Plates were incubated at 30 °C for 30 min. During the incubation period, the MultiScreen harvest plates were pre-wetted with 10% TCA/5% Ppi. 150μl of TCA/PPi was added to all MultiScreen plate wells after pre-wetting. The kinase reaction was stopped via replica transfer of the polypropylene reaction wells into the MultiScreen plates. The plates were incubated at room temperature for 5 min then vacuum harvested and washed with 200 μl TCA/PPi 3-4 times per well, then 100 μl of cocktail per well was added.

Experimental data consisted of eight (8) compound doses in duplicate with ten (10) enzyme control reaction wells (so-called totals) and six (6) background wells. The results

were obtained as percent inhibition (mean with S.D.) over the full compound dose range. IC_{50} potency estimates are determined using a floating inhibition maximum (Imax).

All compounds in the synthetic examples and Tables above were evaluated in the tyrosine kinase assay above using a kinase such as p56 lck and were found to have IC_{50}'s less than 10 μM.

Representative compounds from the examples above were evaluated in the tyrosine kinase assay above using p60 src and were found to have IC_{50}'s less than 10 μM.

Representative compounds from the examples above were evaluated in the tyrosine kinase assay above using PDGFR kinase and were found to have IC_{50}'s less than 10 μM.

Inhibition of IL-2 Production

Inactivation of T cells resulting from inhibition of the tyrosine kinase p56 lck can be measured by inhibition of IL-2 production in Jurkat cells. 96-well flat bottom plates were coated with anti-CD3, clone UCHT1, (Immunotech cat. # 1304) at 4 μg/ml in Phosphate Buffered Saline (PBS), 100 μl/well. The solution was prepared by taking 200 μl of 200 μg/ml anti-CD3 stock/ 10ml PBS. The plate was then incubated at 37°C for 2h. Jurkat cells were pelleted and counted. The cells were resuspended at 2.5 x 10^6 cells/ml in RPMI, 10 % FBS (complete media). Test compounds were diluted from a 5mg/ml DMSO stock directly into complete media.

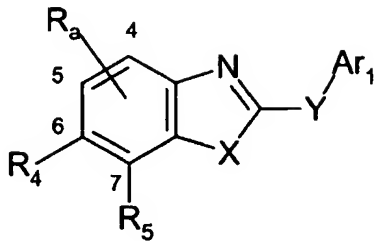
10 μl of 20 X compound/ well was added to a separate plate, followed by 100μl of cell suspension in triplicate and this plate was preincubated at 37°C for 30min. The 96-well plate containing anti-CD3 was aspirated, and the cells and compound transferred to this plate. 100 μl of PMA (Phorbol 12-Myristate 13-Acetate, Sigma cat.# P-8139) at 20 ng/ml was added, and the plate was incubated overnight at 37° C. (PMA stock at 1 mg/ml in ethanol, dilute 10 μl/ml in complete media, then 20 μl/10 mls. in complete media. 100

µl/well = 10 ng/ml. final concentration). The next day, the plate was centrifuged at 1500 rpm for 5 min. at room temperature and the supernatants were removed. The supernatants were tested using R&D Systems Quantikine Human IL-2 Kit (cat.#2050). Samples were diluted 1:5 in RPMI1640, and 100 µl/well used in the ELISA. The optical density of each well was determined using a microplate reader set to 450 nm. EC_{50} values were determined using Origin (non-linear regression) or SAS by plotting absorbance vs. concentration of compound.

Representatives from the synthetic examples and the Tables above were screened in this assay and had IC_{50}'s below 10 µM.

We claim:

1. A Compound of the formula(I):



(I)

wherein:

Ar_1 is an aromatic or nonaromatic carbocycle, heteroaryl or heterocycle; wherein said carbocycle, heteroaryl or heterocycle is optionally substituted by one or more R_1, R_2 and R_3;

X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

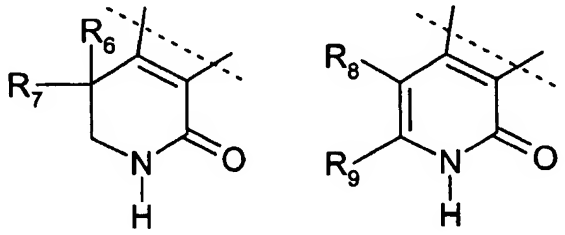
Y is NR_{15}, S or O;

R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl; wherein each R_a is independently optionally substituted with one or more C_{1-6}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5- position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $CONR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$, $(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$; or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H, CN or $CONR_{10}R_{11}$; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10}cycloalkyl, C_{5-7}cycloalkenyl, C_{2-6} alkenyl, C_{2-6} alkynyl each being optionally substituted with one or more C_{3-10}cycloalkyl, C_{3-10}cycloalkylidene, C_{5-7}cycloalkenyl, halogen, OH, oxo, CN, C_{1-3}alkoxy, C_{1-3}acyloxy, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}C(=NR_{10})NR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$, $C(R_{10})=NNR_{10}CONR_{10}R_{11}$, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy, arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl, heteroaryl, or heterocycle, wherein each aryl, heteroaryl or heterocycle is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl or $NR_{10}C(=NR_{10})NR_{10}R_{11}$, C_{1-3}alkoxy, halogen, CN, oxo, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 5 or 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two C_{1-3}alkyl, OH, oxo or $(CH_2)_nNR_{10}R_{11}$, or optionally spiro-fused to a 1,3 dioxolane group or 1,3 dithiolane group, each 1,3 dioxolane group or 1,3 dithiolane group optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, CN, NO_2, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$, and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH, $-(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or heterocycle, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

R_{15} is H or C_{1-3} alkyl;

m is 1-4; n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

2. The compound according to claim 1 wherein

Ar_1 is

a) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl;

b) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cycloheptenyl;

c) phenyl, naphthyl; indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl;

d) heteroaryl selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, benzothiazolyl, quinazolinyl, and indazolyl,or a fused heteroaryl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; or

e) a heterocycle selected from pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl and indolinyl;

wherein each of the above Ar_1 are optionally substituted by one or more R_1, R_2 and R_3;

R_a is H, C_{1-6}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, phenyl or heteroaryl selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, pyrazolyl, imidazolyl, furyl, thiazolyl and thienyl; each R_a being optionally substituted with one or more phenyl, halogen, C_{1-3}alkyl, C_{1-3} alkoxy, OH, oxo, or $NR_{10}R_{11}$; wherein R_a is at the 4- position;

R_1 and R_2 are as hereinabove defined;

R_3 is H, halogen, methyl, methoxy, hydroxymethyl or OH;

R_8 is H, C_{1-3}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$ or $(CH_2)_nCONR_{10}R_{11}$;

R_9 is CN or $CONR_{10}R_{11}$; or R_9 is C_{1-3}alkyl branched or unbranched, C_{2-4} alkenyl, C_{2-4}alkynyl each being optionally substituted with one or more C_{5-7}cycloalkyl, C_{5-7}

cycloalkylidene, C_{5-7}cycloalkenyl,OH, CN, C_{1-3}acyloxy, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}C(=NR_{10})NR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$, $C(R_{10})=NNR_{10}CONR_{10}R_{11}$, aryl or heteroaryl; wherein each aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl,heteroaryl or heterocycle, each optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl or $NR_{10}C(=NR_{10})NR_{10}R_{11}$, C_{1-3}alkoxy, halogen, CN, oxo, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 5 or 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by C_{1-3}alkyl or OH, or optionally spiro-fused to a 1,3 dioxolane group or 1,3 dithiolane group, each 1,3 dioxolane group or 1,3 dithiolane group optionally substituted by C_{1-3}alkyl, C_{1-3}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, benzyl and phenyl; wherein said alkyl, cycloalkyl, benzyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CN, NO_2, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH, $-(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;;

R_{12} is H, C_{1-6}alkyl or C_{5-7}cycloalkyl, each optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or heterocycle, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;

or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$; and

R_{15} is H.

3. The compound according to claim 2 wherein:

Ar_1 is phenyl, or pyridyl, wherein each is optionally substituted by one or more

R_1, R_2 and R_3 as defined below;

X is NH or N-CH_3;

Y is NH and

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl;

R_1 and R_2 are the same or different and selected from: H, halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl are optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is CN; or R_9 is methyl, C_{2-3} alkenyl or C_{2-3} alkynyl, each being optionally substituted with one or more C_{5-7} cycloalkylidene, C_{5-7}cycloalkenyl, OH, CN, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})$=$NNR_{10}R_{11}$ or heteroaryl;

or R_9 is aryl or heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, amino or $CONH_2$;

or R_8 and R_9 together form a cyclopentene ring spiro-fused to a 1,3 dioxolane group, said 1,3 dioxolane group being optionally substituted by C_{1-3}alkyl, C_{1-3}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, C_{5-7}cycloalkyl or phenyl, wherein said alkyl, cycloalkyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, NO_2, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy,OH, $(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-3}alkyl or C_{5-7}cycloalkyl, each optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or is a saturated, 4- to 6-membered nitrogen-containing heterocycle, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;

or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

4. The compound according to claim 3 wherein:

Ar_1 is phenyl;

R_a is H or hydroxymethyl;

R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched or C_{5-7}cycloalkyl, wherein said alkyl or cycloalkyl are optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl, $NR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino; or R_{12} is phenyl or is azetidinyl, pyrrolidinyl or piperidinyl, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy and halogen.

5. A compound according to claim 1, wherein:

Ar_1 is an aromatic or nonaromatic carbocycle, heteroaryl or heterocycle; wherein said carbocycle, heteroaryl or heterocycle is optionally substituted by one or more R_1, R_2 and R_3;

X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

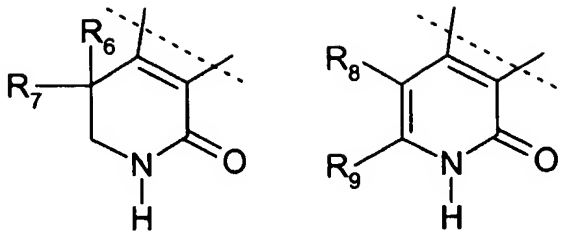
Y is NR_{15}, S or O;

R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl; wherein each R_a is independently optionally substituted with one or more C_{1-3}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl, each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5- position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$, $(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$; or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10}cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl each being optionally substituted with one or more halogen, OH, oxo, CN, C_{1-3}alkoxy, $NR_{10}R_{11}$, $NR_{10}COR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy, arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl or heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two OH, oxo or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$, and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

R_{15} is H or C_{1-3} alkyl;

m is 1-4; n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

6. A compound according to claim 5, wherein:

Ar_1 is

a) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl;

b) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cycloheptenyl;

c) phenyl, naphthyl; indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl;

d) heteroaryl selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, benzothiazolyl, quinazolinyl, and indazolyl,or a fused heteroaryl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; or

e) a heterocycle selected from: pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl and indolinyl;

wherein each of the above Ar_1 are optionally substituted by one or more R_1, R_2 and R_3 as hereinabove defined;

R_a is H, C_{1-6}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, phenyl or heteroaryl selected from: pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, pyrazolyl, imidazolyl, furyl, thiazolyl and thienyl; each R_a being optionally substituted with one or more phenyl, halogen, C_{1-3}alkyl, C_{1-3} alkoxy, OH, oxo, or $NR_{10}R_{11}$; wherein R_a is at the 4- position;

R_3 is H, halogen, methyl, methoxy, hydroxymethyl or OH;

R_8 is H, C_{1-3}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$ or $(CH_2)_nCONR_{10}R_{11}$;

R_9 is C_{1-3}alkyl branched or unbranched, C_{2-4} alkenyl, C_{2-4}alkynyl each being optionally substituted with one or more OH, CN, $NR_{10}R_{11}$, $CONR_{10}R_{11}$, CO_2R_{12}, aryl or heteroaryl; wherein each aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;
or R_9 is aryl or heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by OH;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, benzyl and phenyl; wherein said alkyl, cycloalkyl, benzyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H or C_{1-6}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;

or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$; and

R_{15} is H.

7. The compound according to claim 6 wherein:

Ar_1 is phenyl, or pyridyl;

X is NH or N-CH_3;
Y is NH and

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl;

R_1 and R_2 are the same or different and selected from: halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl are optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is methyl or C_{2-3} alkenyl each being optionally substituted with one or more OH, CN, $NR_{10}R_{11}$, $CONR_{10}R_{11}$ or CO_2R_{12};
or R_9 is heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen or amino;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy or OH;

R_{12} is H or C_{1-3}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

8. The compound according to claim 7 wherein:

Ar_1 is phenyl;

R_a is H or hydroxymethyl;

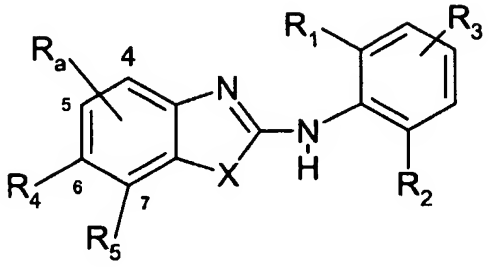
R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;
or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino.

9. A compound of the formula (Ia):



(Ia)

wherein:

X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl;

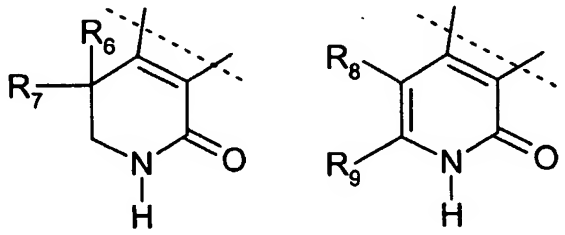
wherein each R_a is independently optionally substituted with one or more C_{1-6}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5-position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10}

branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $CONR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$,

$(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$ or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H, CN or $CONR_{10}R_{11}$; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10}cycloalkyl, C_{5-7}cycloalkenyl, C_{2-6} alkenyl, C_{2-6} alkynyl each being optionally substituted with one or more C_{3-10}cycloalkyl, C_{3-10}cycloalkylidene, C_{5-7}cycloalkenyl, halogen, OH, oxo, CN, C_{1-3}alkoxy, C_{1-3}acyloxy, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, $NR_{10}C(=NR_{10})NR_{10}R_{11}$, $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$, $C(R_{10})=NNR_{10}CONR_{10}R_{11}$, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy, arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_9 is aryl, heteroaryl, or heterocycle, wherein each aryl, heteroaryl or heterocycle is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl or $NR_{10}C(=NR_{10})NR_{10}R_{11}$, C_{1-3}alkoxy, halogen, CN, oxo, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 5 or 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two C_{1-3}alkyl, OH, oxo or $(CH_2)_nNR_{10}R_{11}$, or optionally spiro-fused to a 1,3 dioxolane group or 1,3 dithiolane group, each 1,3 dioxolane group or 1,3 dithiolane group optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, CN, NO_2, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by

O, $S(O)_p$, and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH, $-(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or heterocycle, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

m is 1-4, n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

10. The compound according to claim 9 wherein:

X is NH or N-CH_3;

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl; and wherein R_a is attached at the 4- position;

R_1 and R_2 are the same or different and selected from: H, halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is CN; or R_9 is methyl, C_{2-3} alkenyl or C_{2-3} alkynyl, each being optionally substituted with one or more C_{5-7} cycloalkylidene, C_{5-7}cycloalkenyl, OH, CN, $NR_{10}R_{11}$, $NR_{10}CONR_{10}R_{11}$, , $NR_{10}COR_{12}$, $NR_{10}S(O)_pR_{12}$, $CONR_{10}R_{11}$, CO_2R_{12}, $C(R_{10})=NNR_{10}R_{11}$ or heteroaryl;

or R_9 is aryl or heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, amino or $CONH_2$;

or R_8 and R_9 together form a cyclopentene ring spiro-fused to a 1,3 dioxolane group, said 1,3 dioxolane group being optionally substituted by C_{1-3}alkyl, C_{1-3}alkoxy, OH or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, C_{5-7}cycloalkyl or phenyl, wherein said alkyl, cycloalkyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, NO_2, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy,OH, $(CH_2)_nNR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$;

R_{12} is H, C_{1-3}alkyl or C_{5-7}cycloalkyl, each optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl or is a saturated, 4- to 6-membered nitrogen-containing heterocycle, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

11. The compound according to claim 10 wherein:

R_a is H or hydroxymethyl;

R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched or C_{5-7}cycloalkyl, wherein said alkyl or cycloalkyl are optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl, $NR_{13}R_{14}$, $CONR_{13}R_{14}$ or $NR_{13}COR_{14}$; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino; or R_{12} is phenyl or is azetidinyl, pyrrolidinyl or piperidinyl, each optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy and halogen.

12. The compound according to claim 9, wherein:

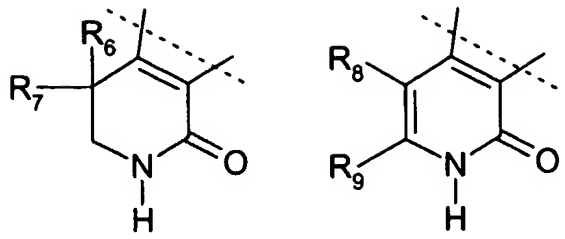
X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl;
wherein each R_a is independently optionally substituted with one or more C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5- position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl, aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formulas A or B:



A B

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_8 is H, C_{1-6}alkyl branched or unbranched, saturated or unsaturated, optionally substituted with phenyl, OH or C_{1-3}alkoxy; or R_8 is $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_mNR_{10}COR_{12}$, $(CH_2)_nCO_2R_{12}$, $(CH_2)_nCONR_{10}R_{11}$ or R_8 is phenyl or heteroaryl, each being optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, OH, $-SO_3H$ or halogen;

R_9 is H; or R_9 is C_{1-10}alkyl branched or unbranched, C_{3-10}cycloalkyl, C_{2-6} alkenyl, C_{2-6}alkynyl each being optionally substituted with one or more halogen, OH, oxo, CN, C_{1-3}alkoxy, $NR_{10}R_{11}$, $NR_{10}COR_{12}$, SR_{12}, $CONR_{10}R_{11}$, CO_2R_{12}, aryloxy, arylthio, aryl or heteroaryl; wherein each aryloxy, arylthio, aryl or heteroaryl is optionally substituted with C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$ or $O(CH_2)_{2-4}NR_{10}R_{11}$;
or R_9 is aryl or heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

or R_8 and R_9 together form a saturated or unsaturated 6 membered aromatic or nonaromatic carbocyclic ring optionally substituted by one or two OH, oxo or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$, and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$;

m is 1-4, n is 0-3 and p is 0-2; and

the pharmaceutically acceptable acid or salt derivatives thereof.

13. The compound according to claim 12 wherein:

X is NH or N-CH_3;

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl; and wherein R_a is attached at the 4- position;

R_1 and R_2 are the same or different and selected from: halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_4 and R_5 together complete a fused ring of formula B;

R_8 is H, C_{1-3}alkyl optionally substituted with OH; or R_8 is $(CH_2)_{2-3}NR_{10}R_{11}$ or CO_2R_{12};

R_9 is methyl or C_{2-3} alkenyl each being optionally substituted with one or more OH, CN, $NR_{10}R_{11}$, $CONR_{10}R_{11}$ or CO_2R_{12};
or R_9 is heteroaryl optionally substituted with one to three groups selected from C_{1-3}alkyl optionally substituted with phenyl, C_{1-3}alkoxy, halogen or $(CH_2)_nNR_{10}R_{11}$;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy or OH;

R_{12} is H or C_{1-3}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

14. The compound according to claim 13 wherein:

R_a is H or hydroxymethyl;

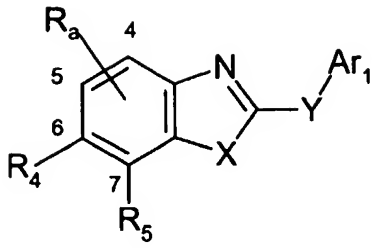
R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;
or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino.

15. An intermediate compound of the formula(III):



(III)

wherein:

Ar_1 is an aromatic or nonaromatic carbocycle, heteroaryl or heterocycle; wherein said carbocycle, heteroaryl or heterocycle is optionally substituted by one or more R_1, R_2 and R_3;

X is NH, N-C_{1-3}alkyl, N-cyclopropyl, S or O;

Y is NR_{15}, S or O;

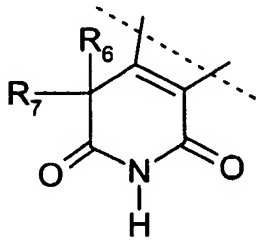
R_a is H, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl, each of which may be branched or cyclic; or R_a is aryl or heteroaryl;
wherein each R_a is independently optionally substituted with one or more C_{1-3}alkyl, C_{1-6} alkoxy, halogen, OH, oxo, $NR_{10}R_{11}$, aryl or heteroaryl, each aryl or heteroaryl being optionally substituted with one or more groups selected from halogen, OH, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl and $(CH_2)_mNR_{10}R_{11}$; and wherein R_a is attached at the 4- or 5-position;

R_1 and R_2 are the same or different and selected from H, halogen, CN, NO_2, C_{1-10} branched or unbranched saturated or unsaturated alkyl, C_{1-10} branched or unbranched alkoxy, C_{1-10} branched or unbranched acyl, C_{1-10} branched or unbranched acyloxy, C_{1-10} branched or unbranched alkylthio, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl, $NR_{10}R_{11}$, aryl, aroyl,

aryloxy, arylsulfonyl, heteroaryl and heteroaryloxy; wherein the abovementioned R_1 and R_2 are optionally partially or fully halogenated or optionally substituted with one to three groups independently selected from oxo, OH, $NR_{10}R_{11}$, C_{1-6} branched or unbranched alkyl, C_{3-7}cycloalkyl, phenyl, naphthyl, heteroaryl, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

R_3 is H, halogen, OH, $(CH_2)_nNR_{10}R_{11}$, $(CH_2)_nCO_2R_{12}$; C_{1-3}alkyl optionally substituted with OH, C_{1-3} alkoxy optionally halogenated or C_{1-3} alkylthio;

R_4 and R_5 together with the atoms to which they are attached complete a fused ring system of the formula C:



C

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, aryl, arylC_{1-3}alkyl and heteroaryl; wherein said alkyl, cycloalkyl, aryl, arylC_{1-3}alkyl or heteroaryl are optionally

substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$, aryl or heteroaryl;

or R_{10} and R_{11} together form a 3-7 member alkylene chain completing a ring about the N atom to which they are attached; wherein said alkylene chain is optionally interrupted by O, $S(O)_p$ and NR_{13}; and wherein said ring is optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H, C_{1-6}alkyl or C_{3-8}cycloalkyl wherein each alkyl or cycloalkyl is optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$; or R_{12} is phenyl, optionally substituted with one to three groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, halogen, $(CH_2)_mNR_{10}R_{11}$, $(CH_2)_nCONR_{10}R_{11}$ and $O(CH_2)_{2-4}NR_{10}R_{11}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with alkoxy, OH or phenyl;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$; and

m is 1-4, n is 0-3 and p is 0-2.

16. The compound according to claim 15 wherein

Ar_1 is

a) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl;

b) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cycloheptenyl;

c) phenyl, naphthyl; indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl;

d) heteroaryl selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, benzothiazolyl, quinazolinyl and indazolyl, or a fused heteroaryl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; or

e) a heterocycle selected from: pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl and indolinyl;

wherein each of the above Ar_1 are optionally substituted by one or more R_1, R_2 and R_3 as hereinabove defined;

R_a is H, C_{1-6}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, phenyl or heteroaryl selected from: pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, pyrazolyl, imidazolyl, furyl, thiazolyl and thienyl; each R_a being optionally substituted with one or more phenyl, halogen, C_{1-3}alkyl, C_{1-3} alkoxy, OH, oxo, or $NR_{10}R_{11}$; wherein R_a is at the 4- position;

R_3 is H, halogen, methyl, methoxy, hydroxymethyl or OH;

R_6 is C_{1-3}alkyl or H;

R_7 is C_{1-6}alkyl branched or unbranched or H;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-6}alkyl branched or unbranched, C_{3-8}cycloalkyl, benzyl and phenyl; wherein said alkyl, cycloalkyl or phenyl are optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy, OH or $-(CH_2)_nNR_{13}R_{14}$;

R_{12} is H or C_{1-6}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-6} alkyl optionally substituted with C_{1-3}alkoxy, OH or phenyl;
and
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

17. The compound according to claim 16 wherein:

Ar_1 is phenyl, or pyridyl;

X is NH or N-CH_3;
Y is NH and

R_a is H, hydroxyC_{1-2}alkyl, 2-hydroxyethylaminomethyl, methoxybenzylaminomethyl, pyridinyl optionally halogenated, phenyl, 3-hydroxy-2-oxo-propyl, vinyl or C_{3-5}alkynyl substituted by C_{1-3}alkoxy or phenyl;

R_1 and R_2 are the same or different and selected from: halogen, C_{1-3} alkyl, wherein the C_{1-3} alkyl are optionally partially or fully halogenated, NO_2, $NR_{13}R_{14}$;

R_3 is H, halogen, methoxy or methyl;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, C_{1-3}alkoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, C_{1-3}alkoxy, C_{1-3}acyloxy, CO_2R_{12}, $NR_{13}R_{14}$, $O(CH_2)_{2-4}NR_{13}R_{14}$ or phenyl;

or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-3} alkyl, C_{1-3}alkoxy or OH;

R_{12} is H or C_{1-3}alkyl optionally substituted with phenyl, OH, C_{1-3}alkoxy or $NR_{13}R_{14}$;

R_{13} and R_{14} are each independently selected from H and C_{1-3}alkyl optionally substituted with C_{1-3}alkoxy or OH;
or R_{13} and R_{14} together form a chain completing a ring, said chain is $(CH_2)_{4-5}$ or $(CH_2)_2O(CH_2)_2$.

18. The compound according to claim 17 wherein:

Ar_1 is phenyl;

R_a is H or hydroxymethyl;

R_1 and R_2 are the same or different and selected from: halogen, methyl optionally partially or fully halogenated, NO_2 and NH_2;

R_3 is H, chloro, fluoro, bromo or methoxy;

R_{10} and R_{11} may be the same or different and are each independently selected from H, OH, methoxy, C_{1-3}alkyl branched or unbranched, optionally substituted with OH, $NR_{13}R_{14}$ or phenyl;
or R_{10} and R_{11} together form morpholino, pyrrolidinyl, piperazinyl or piperidinyl each optionally substituted by C_{1-2} alkyl; and

R_{12} is C_{1-3}alkyl optionally substituted with morpholino.

19. A compound selected from the group consisting of:

2-(2,6-Dichlorophenylamino)-3,5-dihydro-imidazo[4,5-i]phenanthridin-4-one;

2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-hydroxyethyl)-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-h]isoquinoline-6-carboxylic acid methyl ester;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylic acid methyl ester;

2-(2-Chloro-6-methylphenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-N-methoxy-N-methylacrylamide;

2-(2-Chloro-6-nitrophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

N-Benzyl-3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylamide;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylic acid 4-morpholine amide;

2-(2,6-Dichlorophenylamino)-4-hydroxymethyl-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-vinyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-h]isoquinoline-6- carboxylic acid 2-(4-moropholino)ethyl ester;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-hydroxypropen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-vinyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-morpholin-4-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

3-[2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylonitrile;

2-(2-Chloro-6-methylphenylamino)-1,7-dimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2-Chloro-6-methylphenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-pyrrolidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(4-methylpiperazin-1-yl-propen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-piperidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-{3-[ethyl(2-hydroxyethyl)amino]propen-1-yl}-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

7-(3-Diethylaminopropen-1-yl)-1,6-dimethyl-2-(2,6-dimethylphenylamino)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-{3-[(2-diethylaminoethyl)methylamino]-propen-1-yl}-1,6-dimethyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

7-(3-Diethylaminopropen-1-yl)-1,6-dimethyl-2-(2,4,6-trichlorophenylamino)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-6-methyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(2-pyrrolidin-1-ylmethylpyrrolidin-1-yl)-propen-1-yl]-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

7-[3-(2*S*-Aminomethylpyrrolidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

1-{3-[2-(2,6-Ddichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-*L*-proline carboxamide;

1-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-3-carboxamide;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(methylhydrazonomethyl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

7-[3-(3-Aminopyrrolidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(3-acetamidopyrrolidin-1-yl)-propen-1-yl]- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-[3-(3-dimethylaminopyrrolidin-1-yl)-propen-1-yl]- 1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

1-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-2-carboxamide;

7-[3-(3-Aminomethylpiperidin-1-yl)-propen-1-yl]-2-(2,6-dichlorophenylamino)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-*h*]-isoquinolin-9-one;

1-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-piperidine-3-carboxylic acid diethylamide;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-ethynyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

1-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-3-methyl urea;

Cyclohexane carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide;

2-(2,6-Dichlorophenylamino)-1-methyl-7-phenyl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl} methanesulfonamide;

3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl urea;

1-Cyclohexyl-3-{3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-urea;

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl} benzenesulfonamide;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-ethylaminopropen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

N-{3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1*H*-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}-guanidine;

Piperidine-3-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide;

L-Proline {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide;

D-Proline {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide;

3-[2-(2,6-Dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-benzamide;

L-Azetidine-2-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide;

Piperidine-2-carboxylic acid {3-[2-(2,6-dichlorophenylamino)-1,6-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-propenyl}amide; and

the pharmacuetically acceptable derivatives thereof.

20. A compound according to claim 19 selected from the group consisting of:

2-(2,6-Dichlorophenylamino)-3,5-dihydro-imidazo[4,5-i]phenanthridin-4-one;

2-(2,6-Dichlorophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-6-(2-hydroxyethyl)-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-h]isoquinoline-6- carboxylic acid methyl ester;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylic acid methyl ester;

2-(2-Chloro-6-methylphenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-N-methoxy-N-methylacrylamide;

2-(2-Chloro-6-nitrophenylamino)-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

N-Benzyl-3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylamide;

3-[2-(2,6-Dichlorophenylamino)-1-methyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylic acid 4-morpholine amide;

2-(2,6-Dichlorophenylamino)-4-hydroxymethyl-1,6,7-trimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-vinyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-1,8-dihydro-imidazo[4,5-h]isoquinoline-6- carboxylic acid 2-(4-moropholino)ethyl ester;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-hydroxypropen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-vinyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-morpholin-4-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

3-[2-(2,6-Dichlorophenylamino)-1,7-dimethyl-9-oxo-8,9-dihydro-1H-imidazo[4,5-h]isoquinolin-7-yl]-acrylonitrile;

2-(2-Chloro-6-methylphenylamino)-1,7-dimethyl-1,8-dihydro-imidazo[4,5-h]isoquinoline-9-one;

2-(2,6-Dichlorophenylamino)-1-methyl-7-oxazol-5-yl-1,8-dihydro-imidazo[4,5-h]isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2-Chloro-6-methylphenylamino)-7-(3-hydroxypropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1,6-dimethyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-pyrrolidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-(3-diethylaminopropen-1-yl)-1-methyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(4-methylpiperazin-1-yl-propen-1-yl)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-(3-piperidin-1-yl-propen-1-yl)- 1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-1,6-dimethyl-7-{3-[ethyl(2-hydroxyethyl)amino]propen-1-yl}-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

7-(3-Diethylaminopropen-1-yl)-1,6-dimethyl-2-(2,6-dimethylphenylamino)-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one;

2-(2,6-Dichlorophenylamino)-7-{3-[(2-diethylaminoethyl)methylamino]-propen-1-yl}-1,6-dimethyl-1,8-dihydro-imidazo[4,5-h]-isoquinolin-9-one; and

the pharmaceutically acceptable derivatives thereof.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 1, 9, 15 or 19.

22. A method of treating an autoimmune disease or cancer, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claims 1, 9, 15 or 19.

23. A method according to claim 22, wherein the autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, systemic lupus erythematosus, insulin-dependent diabetes mellitus and asthma.

24. A method according to claim 22, wherein the cancer is selected from a src-dependent tumor or a PDGF-dependent tumor.

25. A method according to claim 24, wherein the src-dependent tumor is selected from mammary carcinoma, colon carcinoma, melanoma and sarcoma.

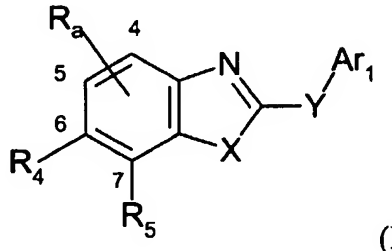
26. A method according to claim 24, wherein the PDGF-dependent tumor is selected from ovarian cancer, prostate cancer and glioblastoma.

27. A method of treating a disease selected from osteoporosis, Paget's disease, bone inflammation, and joint inflammation , said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claims 1, 9, 15 or 19.

28. A method of treating a disease selected from fibrotic diseases, restenosis and atherosclerosis, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claims 1, 9, 15 or 19.

29. A method of enhancing or potentiating the effectiveness of radiation therapy by administering to a patient undergoing such therapy a therapeutically effective amount of compound according to claims 1, 9, 15 or 19.

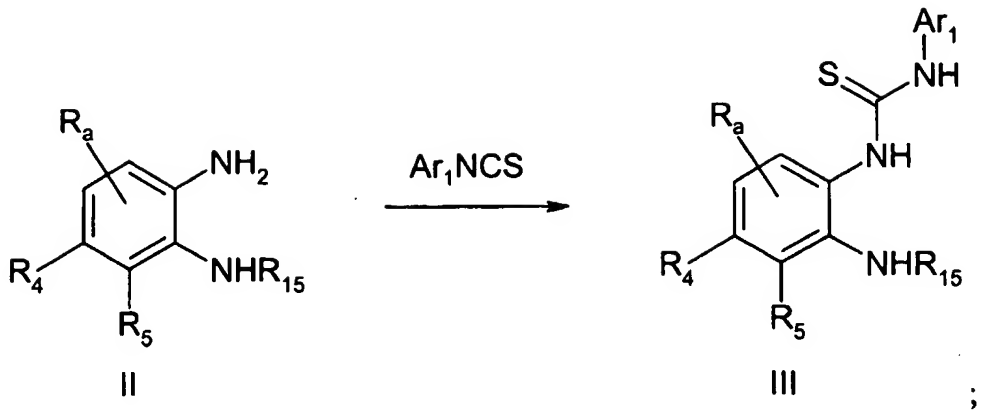
30. A method of making a compound of the formula(I)



(I)

wherein X is N-R_{15} and Ar_1, R_4, R_5, R_{15} and R_a are as defined in claim 1, said process comprising:

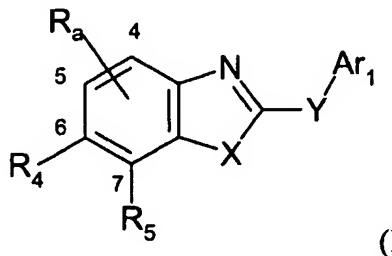
a) reacting a compound of the formula(II) with Ar_1NCS in a suitable solvent at about ambient to reflux temperature for about 3 to 24 hr to provide a compound of the formula(III);



II III ;

b) reacting the product (II) of step a) with a suitable activating agent chosen from 1,3-dicyclohexylcarbodiimide (DCC) and mercuric oxide in a suitable solvent at about ambient to reflux temperature to form a compound of the formula(I) as shown above or precursors thereof.

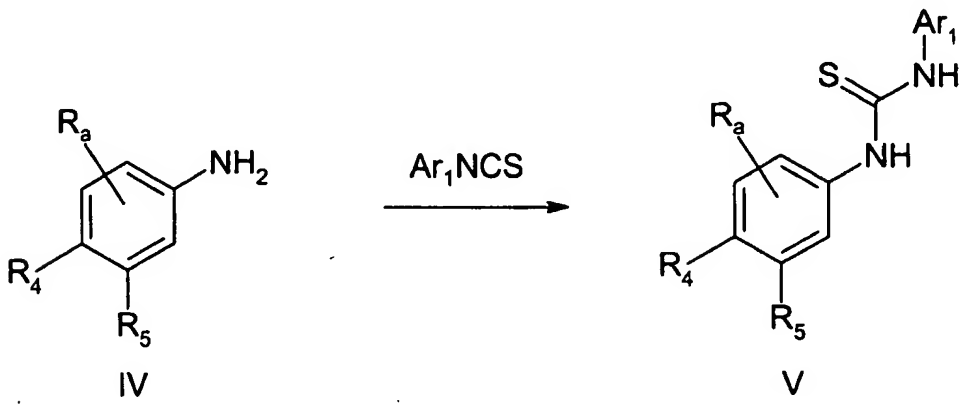
31. A method of making a compound of the formula(I)



(I)

wherein X is S, Y is NH and Ar_1, R_4, R_5 and R_a are as defined in claim 1, said process comprising:

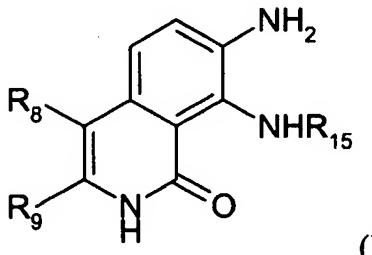
a) reacting a compound of the formula(IV) with Ar_1NCS in a suitable solvent at about ambient to reflux temperature for about 3 to 24 hr to form a compound of the formula(V);



IV V

b) reacting the product(V) of step a) under cyclizing conditions in a suitable solvent at about reflux temperature to form a compound of the formula(I) or a precursor thereof.

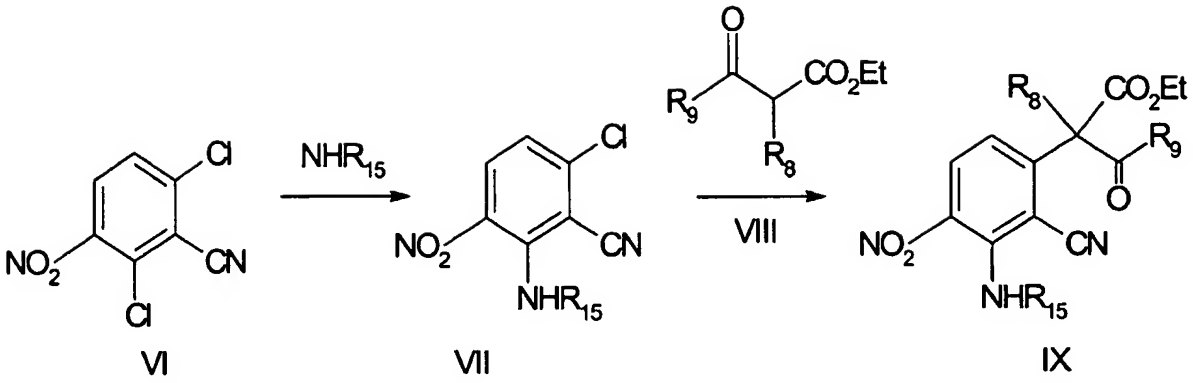
32. A method of making a compound of the formula(XI) wherein R_{15}, R_8 and R_9 are as described in claim 1:



(XI);

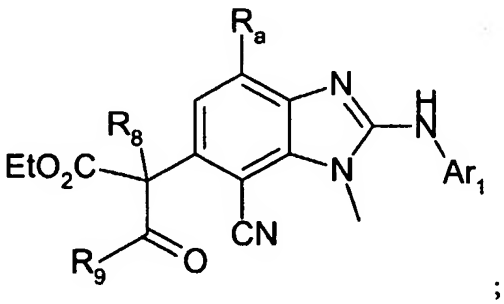
said method comprising:

a) reacting a compound of the formula(VI) with NHR_{15} in a suitable solvent optionally in a pressure flask and at about 0 to 80 ^{o}C, to provide VII, and subsequently reacting compound VII with keto-ester VIII in the presence of a suitable base in a suitable solvent, at about ambient temperature to form a compound of the formula(IX.):



b) hydrolyzing the product of step a) by reacting with aqueous acid, and cyclizing at about reflux temperature; followed subsequently reducing the cyclized product in a suitable solvent to form a compound of the formula(XI).

33. A method of making a compound of the formula:

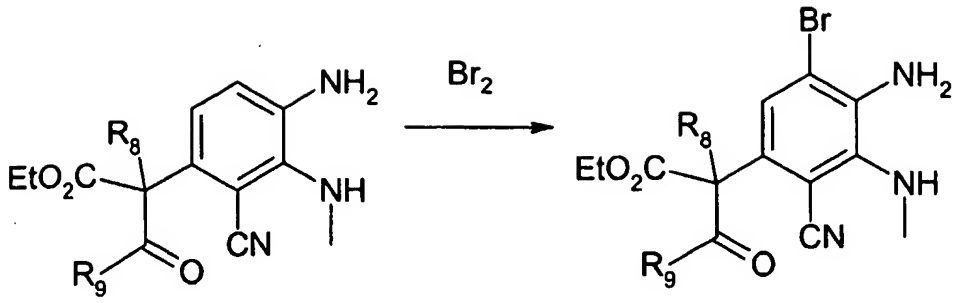


;

wherein R_a, R_8, R_9 and Ar_1 are as described in claim 1;

said method comprising:

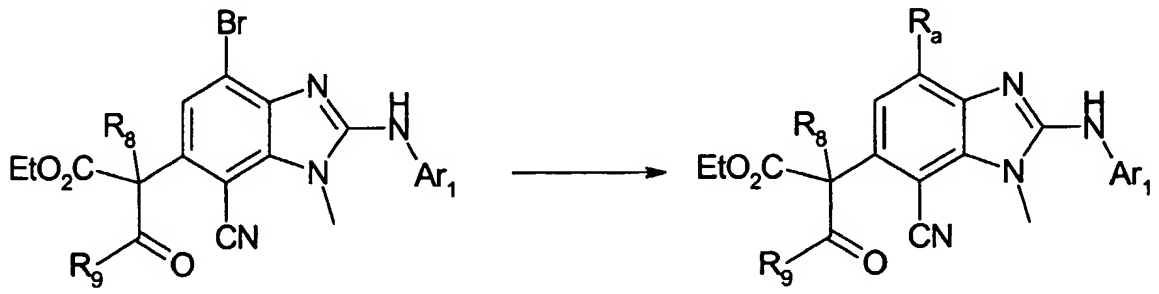
a) reacting a compound of the formula(XII) with bromine in a suitable solvent at ambient temperature to provide XIII.



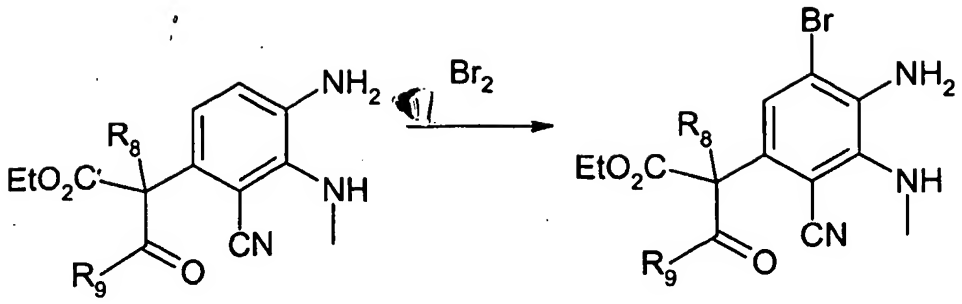
XII XIII

b) reacting a compound of the formula(XIII) with Ar_1NCS in a suitable solvent at about ambient to reflux temperature for about 3 to 24 hr and subsequently reacting the product with a suitable activating agent chosen from 1,3-dicyclohexylcarbodiimide (DCC) and mercuric oxide in a suitable solvent at about ambient to reflux temperature to form a compound of the formula(XIV);

c) cross-coupling to introduce R_a in place of bromine in the presence of a suitable catalyst in a suitable solvent at about 100 ^oC, to form the product compound shown below:



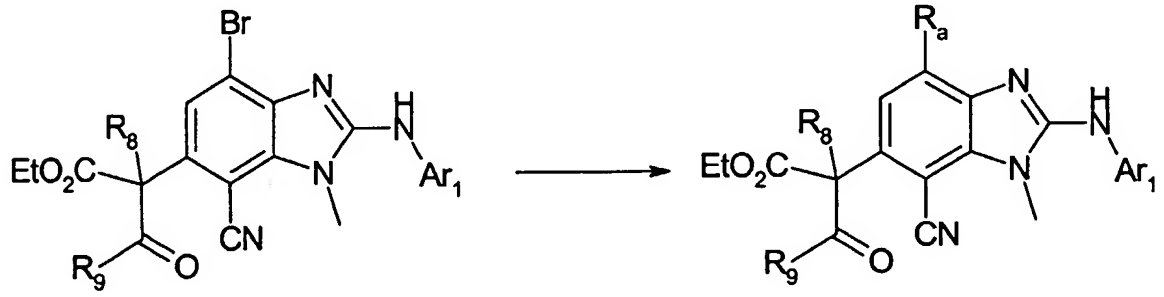
XIV



XII XIII

b) reacting a compound of the formula(XIII) with Ar_1NCS in a suitable solvent at about ambient to reflux temperature for about 3 to 24 hr and subsequently reacting the product with a suitable activating agent chosen from 1,3-dicyclohexylcarbodiimide (DCC) and mercuric oxide in a suitable solvent at about ambient to reflux temperature to form a compound of the formula(XIV);

c) cross-coupling to introduce R_a in place of bromine in the presence of a suitable catalyst in a suitable solvent at about 100 ^oC, to form the product compound shown below:



XIV

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25238 A3

(51) International Patent Classification[7]: C07D 471/04, 513/04, 498/04, A61K 31/437, 31/4355, A61P 35/00, C07D 217/24 // (C07D 471/04, 235:00, 221:00) (C07D 513/00, 277:00, 221:00)

(21) International Application Number: PCT/US00/27444

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/157,922 6 October 1999 (06.10.1999) US

(71) Applicant: **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.** [US/US]; 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).

(72) Inventors: **SNOW, Roger, John**; 29 East Gate Road, Danbury, CT 06811 (US). **CARDOZO, Mario, Gustavo**; 3 Apache Drive, Brookfield, CT 06804 (US). **GOLDBERG, Daniel**; 284 Main Street, New Canaan, CT 06840 (US). **HAMMACH, Abdelhakim**; 8 Rolf's Drive, Danbury, CT 06810 (US). **MORWICK, Tina**; 114 Taylor Road, New Milford, CT 06776 (US). **MOSS, Neil**; 199 Barlow Mountain Road, Ridgefield, CT 06877 (US). **PATEL, Usha, R.**; 20 Dairy Farm Drive, Brookfield, CT 06804 (US). **PROKOPOWICZ, Anthony, S., III**; 11 Quogue Road, Patterson, NY 12563 (US). **TAKAHASHI, Hidenori**; 68 Ehmer Drive, LaGrangeville, NY 12540 (US). **TSCHANTZ, Matt, Aaron**; 58 Sugar Lane, Newtown, CT 06470 (US). **WANG, Xiao-jun**; 50 Judith Drive, Danbury, CT 06811 (US).

(74) Agents: **RAYMOND, Robert, P.** et al.; Boehringer Ingelheim Corporation, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US).

(81) Designated States *(national)*: CA, JP, MX.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

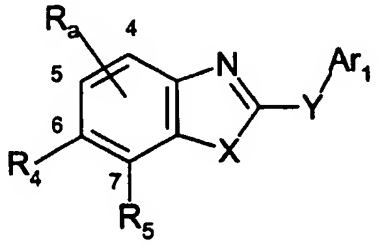
Published:
— *with international search report*

(88) Date of publication of the international search report:
25 October 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/25238 A3

(54) Title: HETEROCYCLIC COMPOUNDS USEFUL AS INHIBITORS OF TYROSINE KINASES



(I)

(57) Abstract: Disclosed are novel compounds of formula (I) wherein Ar_1, R_a, R_4, R_5, X and Y are defined below, which are useful as inhibitors of certain protein tyrosina kinases and are thus useful for treating diseases associated with such kinases, for example, diseases resulting from inappropriate cell proliferation, which include autoimmune diseases, chronic inflammatory diseases, allergic diseases, transplant rejection and cancer. Also disclosed are processes for preparing these compounds, novel intermediates useful in these processes and compositions comprising compounds of formula (I).

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/US 00/27444

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D513/04 C07D498/04 A61K31/437 A61K31/4355
A61P35/00 C07D217/24 C07D491/20 C07D235/30
//(C07D471/04,235:00,221:00),(C07D513/04,277:00,221:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	DE 27 32 951 A (DR. KARL THOMAE GMBH) 8 February 1979 (1979-02-08) page 12 -page 14; claim 1	1,22
A	US 4 176 184 A (BOEHRINGER INGELHEIM GMBH) 27 November 1979 (1979-11-27) cited in the application column 18 -column 20; claim 1; examples 1,13	1,22
A	EP 0 322 746 A (ORION CO., LTD) 29 May 1996 (1996-05-29) cited in the application claims 3,4,11	1,22

-/--

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2001	12/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Alfaro Faus, I

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Intern. ial Application No
PCT/US 00/27444

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D491/20,317:00,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 646 153 A (SPADA, A. P. ET AL.) 8 July 1997 (1997-07-08) abstract; claim 1, column 60, lines 45-52: isoquinolinone	1,22
A	WO 99 24035 A (BISTOL-MEYERS SQUIBB CO.) 20 May 1999 (1999-05-20) cited in the application abstract; claim 1	1,22

☐ Further documents are listed in the continuation of box C.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

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